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THE TRUTH ABOUT PEDIATRIC ANTIDEPRESSANT USE

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ABSTRACT

In 2003, the FDA discovered that a number of clinical-trial adverse events from a pediatric study of the antidepressant drug Paxil involved suicidal behavior or ideation. In response, in June 2003, the FDA issued a public health advisory recommending against the use of Paxil as a pediatric antidepressant. In October of the same year, the FDA commissioned patient-level data sets from a number of antidepressant-medication manufacturers in order to have a larger set of data from which to draw conclusions about the association between pediatric use of antidepressant drugs and increased risk of suicidality. Also in October 2003, the FDA issued the first in a series of health advisories warning of an association between the use of pediatric antidepressants generally and an increase risk of suicidality. After rigorously analyzing the data from the drug-manufacturer studies, the FDA reached the conclusion that the data in aggregate indicated an increased risk of suicidality in pediatric patients. Therefore, in October 2004, the FDA announced that it would require all antidepressant medication labeling to include a black-box warning describing the increased risk of suicidality in children and adolescents. Unfortunately, by 2005, researchers documented 20-30% declines in antidepressant use by children and adolescents and a concurrent increase in the national adolescent suicide rate. Paradoxically, by attempting to protect America's youth from an increased risk of *suicide ideation and behavior*, the FDA inadvertently steered vulnerable individuals away from much-needed treatment, thereby, increasing their risk of *actual suicide*. This paper explores the disorder of major depression, surveys the data on pediatric antidepressant use and suicidality, and evaluates the FDA's actions in light of the unintended consequences. This paper seeks to answer the question: when faced with a medication side effect that is also a symptom of the disease, what was the FDA to do?

THE TRUTH ABOUT PEDIATRIC ANTIDEPRESSANT USE

Side effects associated with antidepressant medications may include headache, nausea, insomnia, nervousness, agitation, sexual problems, dry mouth, constipation, bladder problems, blurred vision, drowsiness... and increased risk of suicide ideation in children, adolescents, and young adults.¹ In an effort to fully inform the public, in October 2004, the U.S. Food and Drug Administration (FDA) mandated that the makers of all antidepressant medications include a black-box warning on their products' labeling detailing the "increased risks of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months)."² The black-box warning, as well as the various FDA public addresses leading up to the black-box warning, did not go unnoticed: "By 2005, researchers documented 20-30% declines in antidepressant use by children and adolescents,...[accompanied by] a concurrent increase in the national adolescent suicide rate, although no causal association has been documented."³ Given the strength and repetition of the FDA's warnings, such a response is in no way surprising; it is no wonder that an increased risk of suicidality, which sounds confusingly similar to an increased risk of committing suicide, would be too much for children, adolescents, young adults, and their parents to bear.

Paradoxically, by attempting to protect America's youth from an increased risk of *suicide ideation and behavior*, the FDA inadvertently steered vulnerable individuals away from much-needed treatment, thereby, increasing their risk of *actual suicide*. In hindsight, some have argued

¹ National Institute of Mental Health, *Depression*, <http://www.nimh.nih.gov/health/publications/depression/complete-index.shtml> (last visited January 20, 2011).

² U.S. FOOD & DRUG ADMIN., ANTIDEPRESSANT USE IN CHILDREN, ADOLESCENTS, AND ADULTS (MAY 2, 2007). See also U.S. FOOD & DRUG ADMIN., REVISIONS TO PRODUCT LABELING, <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM173233.pdf> (last visited January 20, 2011).

³ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11, 11 (2010).

that the FDA's public addresses and black-box warning were counter-productive. But when faced with this conundrum of a medication side effect that is also a symptom of the disease, what was the FDA to do? Would it have been proper for the FDA to censor the drug study findings regarding increased suicide ideation in an act of paternalism? Could the FDA have framed the information in a way that would be less "scary" to the public, but still effective in communicating the significance of the message? When faced with this incredibly difficult situation, what should the FDA have done to best fulfill its mission of promoting the public health and safety?

I. DEPRESSION IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA, explains,

Depression is a serious mental illness that affects the way nearly 19 million adult Americans feel, think, and interact. While everyone experiences occasional sadness, particularly in response to loss or adversity, a person with depression has persistent symptoms that can significantly interfere with their ability to function. People with depression cannot merely 'pull themselves together' and get better. Depression cannot be willed or washed away.⁴

Symptoms of depression include:

persistently sad, anxious or empty moods; loss of pleasure in usual activities (anhedonia); feelings of helplessness, guilt, or worthlessness; crying, hopelessness, or persistent pessimism; fatigue or decreased energy; loss of memory, concentration, or decision-making capability; restlessness, irritability; sleep disturbances; change in appetite or weight; physical symptoms that defy diagnosis and do not respond to treatment (especially pain and gastrointestinal complaints); thoughts of suicide, death, or suicide attempts; [and] poor self-image or esteem (as illustrated, for example, by verbal self-reproach).⁵

⁴ *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 67 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

⁵ Louise B. Andrew, *Depression and Suicide*, MEDSCAPE REFERENCE: DRUGS, CONDITIONS & PROC., updated Oct. 21, 2010, <http://emedicine.medscape.com/article/805459-overview> (last visited January 20, 2011).

While the previous list of symptoms may seem to describe the occasional experiences of unaffected individuals, in depressed individuals these symptoms occur concomitantly, and with much greater frequency, duration, and intensity. More specifically, “[t]o establish the diagnosis of major depression, a patient must express one of the first 2 and at least 5 of the other symptoms listed above. Such disturbances must be present nearly daily for at least 2 weeks. Symptoms can last for months or years.”⁶ Because depression involves thoughts and feelings that are experienced by the masses (albeit not to the same extent),

[a]s many as two thirds of the people with depression do not realize that they have a treatable illness and do not seek treatment. Only 50% of persons diagnosed with major depression receive any kind of treatment, and only 20% of these receive treatment consistent with the current practice guidelines of the American Psychiatric Association (APA). *More alarming, in a recent Canadian study, 48% of patients who have suicidal ideation and 24% of those who made a suicide attempt report not receiving care or even perceiving the need for care* (emphasis added).⁷

These statistics are even more frightening when paired with the fact that “[r]esearch conducted at the NIMH indicates that over 90 percent of people who commit suicide have depression or other diagnosable mental or substance disorder.”⁸ Therefore, the under-diagnosis and under-treatment of depression puts these suffering individuals at great risk of self-harm. Unfortunately, the “[p]ersistent ignorance and misperceptions of the disease by the public, and even some health providers, as a personal weakness or failing that can be willed or washed away....[and the] painful stigmatization... of the diagnosis” only exacerbate this problem.⁹

⁶ *Id.*

⁷ *Id.*

⁸ *Mental Illness and Brain Disease: Dispelling Myths and Promoting Recovery through Awareness and Treatment: Hearing Before the Subcomm. on Health of the Comm. on Energy and Com.*, 109th Cong 2 (2006) (statement of Rep. Deal, Member, House Comm. on Energy and Com.).

⁹ Louise B. Andrew, *Depression and Suicide*, MEDSCAPE REFERENCE: DRUGS, CONDITIONS & PROC., updated Oct. 21, 2010, <http://emedicine.medscape.com/article/805459-overview> (last visited January 20, 2011).

Despite the fact that “[d]epression in children is a serious mental illness that affects up to 2.5 percent of children and 8 percent of teenagers,”¹⁰ it is even more likely to go undiagnosed than adult depression because “...behaviors associated with depressive disorders may be seen as normal mood swings typical of a particular developmental stage.”¹¹ Moreover, the unshakable stigma that accompanies mental disorders makes “health care providers...reluctant to prematurely ‘label’ a young person with a mental illness diagnosis.”¹² As a result, symptoms in children are less likely to be recognized as indicia of depression, and even if recognized, health care providers may be more hesitant to prescribe treatment for depression, because in doing so, they must burden a child with a life-long mental illness diagnosis.

As is the case with adult depression, the reality of under-diagnosis and under-treatment of child and adolescent depression leaves a large number of mentally ill youth without the medical attention they so desperately need. One problem with this is that “depression itself impacts the developing brain. Allowing depression to go untreated significantly delays improvement, thereby increasing the likelihood of long-term negative outcomes.”¹³ Another is adolescent suicide. The statistics on adolescent suicide paint a bleak picture: “In the U.S. there are about 1600 suicides in teenagers per year, many of them in people who are diagnosed as having depression.”¹⁴ The magnitude of this number is evidenced by the fact that “[s]uicide is the third leading cause of death in U.S. in this age group [15-19] and accounts for more deaths in this age

¹⁰ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 64 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

¹¹ *Id.* at 68.

¹² *Id.*

¹³ U.S. FOOD & DRUG ADMIN., ACNP COMMENTS ON SSRI USE IN ADOLESCENTS 1, 1 (2004).

¹⁴ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 64 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

group than all other major physical conditions combined.”¹⁵ Large community studies, including the Youth Risk Behavior Study carried out by the National Center for Health Services, have revealed that

[a]lmost 20 percent of American high school students think about suicide. Suicide attempts are also very common. Experts report that the overall rate is about nine percent. Only about a quarter of these attempts are brought to medical attention. It is widely recognized that adolescents are frequently reluctant to disclose suicidal thoughts or even suicide attempts to parents or others. There are about 4,000 female suicide attempts for every female suicide death, and about 400 male attempts for every male death.¹⁶

Depressed youth who “are not identified and treated are likely to have ongoing problems in school, at home and with their friends. Research indicates that more than half will eventually attempt suicide, and an estimated 2 to 5 percent will ultimately die as a result.”¹⁷ Therefore, the recognition and treatment of pediatric depression is absolutely critical to the welfare and survival of our youth.

There is hope, however. Analyses of trends in child and adolescent suicide rates have shown that

[t]he rate of [pediatric suicide] has fallen by about 25 percent over the last decade [~1993-2003], the period in which the use of anti-depressants has grown steadily. The association does not prove that the increasing use of anti-depressants is the cause of the decline in suicide, but it is at least suggestive.¹⁸

II. TREATMENT OPTIONS

¹⁵ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 68 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

¹⁶ *Id.*

¹⁷ *FDA’s Drug Approval Process: Up to the Challenge?: Hearing Before the Comm. on Health, Educ., Lab., and Pensions*, 109th Cong. 44 (2005) (statement of Dr. David Fassler, Board certified child and adolescent psychiatrist, member of the Board of Trustees for the American Psychiatric Association (APA), Clinical Associate Professor of Psychiatry at the University of Vermont).

¹⁸ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 68 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

Depressed children, adolescents, and young adults, like adults, benefit from the standard treatments of antidepressant medication and talk therapy. Dr. David Fassler, a Board Certified child and adolescent psychiatrist and member of the Board of Trustees for the American Psychiatric Association (APA), discusses the treatment of pediatric depression:

Medication, specifically antidepressants, can be helpful, and even lifesaving for some children who have complex psychiatric disorders such as depression. Medication is most effective when it is used as part of a comprehensive treatment plan, individualized to the needs of the child and family... Findings from the NIMH-supported Treatment of Adolescents with Depression Study (TADS) shows that a combination of medication and therapy, specifically, Cognitive Behavioral Therapy, or CBT, are more effective than either option used alone.¹⁹

Just as CBT is the preferred psychotherapy for depressed youths, selective serotonin reuptake inhibitors (SSRIs) are the preferred class of antidepressants for this age group. Dr. Fassler affirms, “Many psychiatrists, patients and families have found the SSRI antidepressants to be extremely helpful for children and adolescents with depression when they are used in a well-monitored treatment program.”²⁰ There are two primary reasons why SSRIs are preferable to the older generations of antidepressants for the treatment of pediatric depression. First, older medications, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs),

can be difficult to tolerate due to significant side effects. MAOI use may also be subject to dietary and medication restrictions. TCAs and MAOIs are of limited value in the pediatric population because of serious, potentially life-threatening adverse events. These include tachycardia, convulsions, and shock-like coma. Moreover, TCAs are a potential tool for adolescents attempting to commit suicide because overdose can cause serious and protracted cardiac arrhythmias. Newer medications, such as the selective serotonin uptake inhibitors (SSRIs), have fewer side effects than the older drugs, making it easier for people to continue treatment.²¹

¹⁹ *FDA’s Drug Approval Process: Up to the Challenge?: Hearing Before the Comm. on Health, Educ., Lab., and Pensions*, 109th Cong. 44 (2005) (statement of Dr. David Fassler, Board certified child and adolescent psychiatrist, member of the Board of Trustees for the American Psychiatric Association (APA), Clinical Associate Professor of Psychiatry at the University of Vermont).

²⁰ *Id.*

²¹ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 68 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

Second, the only antidepressant medication approved by the FDA for use in children and adolescents is an SSRI: Prozac.²² Dr. Temple explains,

Because Prozac is the only product for which efficacy has been established for treatment of pediatric/adolescent MDD [Major Depressive Disorder], it is often the first product prescribed by a physician. However, in 30-40 percent of the cases, Prozac does not work for the patient. In such cases, it is standard care for physicians to prescribe one of the other current generation anti-depressants approved for adults. The older medications, tricyclic anti-depressants (TCAs) and monoamine oxidase inhibitors (MAOIs), have not been approved for use in pediatric/adolescent populations²³.... Additionally, the history of pediatric MDD studies with the tricyclic anti-depressants (TCAs) is uniformly negative. This finding may have several possible explanations, including flaws in study design or conduct, or the possibility that TCAs simply do not work in pediatric MDD.²⁴

The question then becomes, why are other current-generation SSRIs being prescribed to children despite the lack of FDA approval for their use in the pediatric population? Dr. Temple answers this question as well,

Many people have expressed concerns about pediatric use of products approved for MDD in adults where clinical trials in children were negative.... To date, clinical trials evaluating six other current generation anti-depressants approved for adults have not met FDA's standards for establishing efficacy in the child/adolescent population. Nevertheless, there is widespread belief among treating physicians that these products do in fact work and that the "negative" results are in fact inconclusive. Negative trials are not necessarily informative in MDD trials because they may be an indication of inadequate trials rather than evidence of benefit.²⁵

More specifically,

There are many reasons, other than lack of effectiveness, for studies to fail to show benefit. This phenomenon is a particular problem in depression, and even more so in pediatric depression. To begin with, in adult MDD programs for drugs approved for this indication, the overall failure rate for studies that appear in every respect to be adequate trials is about 50 percent. This indicates that showing effectiveness in depression is not easy... It is also possible, ...that there is even greater heterogeneity among pediatric patients who meet criteria for MDD than is true for adults. If true, this would also work against study success in pediatric MDD. Finally, the context in which sponsors conducted these studies may not have been ideal...the failure of a drug registration trial

²² *Id.* at 70.

²³ *Id.*

²⁴ *Id.* at 79.

²⁵ *Id.* at 70.

to show drug effect represents a more significant loss for the sponsor (i.e., the non-approval of the drug) than the failure of a study in response to a Written Request.²⁶

Dr. David E. Wheadon, Senior Vice President of US Regulatory Affairs at GlaxoSmithKline

echoes Dr. Temple's defense of the drugs that have yet to show efficacy in pediatric populations:

Our three trials in pediatric depression as a group did not...provide sufficient evidence that Paxil is more effective than placebo, although we did see some signs of efficacy in our first pediatric depression trial. It is important to note that even for known effective, approved antidepressants, 4 out of 10 studies failed to demonstrate efficacy because of the high placebo response rates seen in these studies....One possible explanation for the outcome of our pediatric depression trials was the high placebo response rate, which made it difficult for the drug to show statistically significant efficacy. Our trials showed a high response rate to Paxil but also a high response rate to placebo – as is common in clinical trials for depression – so it was difficult to demonstrate a statistically significant difference between the two. Another impediment to measuring efficacy in the pediatric population is the need for more refined scales for measuring antidepressant efficacy in this population.²⁷

Jeffrey Bridge, Ph.D., Investigator in the Center for Innovation in Pediatric Practice and Associate Professor at The Ohio State University College of Medicine, and his co-authors lend support to these assertions by detailing their positive findings on efficacy. They explain, “[t]his meta-analysis of all available randomized clinical trials of antidepressant treatment of pediatric MDD, OCD [Obsessive Compulsive Disorder] and non-OCD anxiety disorders shows evidence of efficacy for all 3 indications, although the effects were strongest for non-OCD anxiety disorders, intermediate for OCD, and more modest in MDD.”²⁸ Furthermore, they state, “...we believe that the strength of evidence presented here supports the cautious and well-monitored use of antidepressant medications as one of the first-line treatment options....”²⁹ Robert Gibbons,

²⁶ *Id.* at 78-79.

²⁷ *Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 53 (2004) (statement of Dr. David E. Wheadon, Senior Vice President of U.S. Regulatory Affairs at GlaxoSmithKline).

²⁸ Jeffrey A. Bridge et al., *Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials*, 297(15) J. AMER. MED. ASS'N 1683, 1692 (2007).

²⁹ *Id.* at 1694.

Ph.D., Director of the Center for Health Statistics and Professor of Biostatistics and Psychiatry at the University of Illinois at Chicago, et al. also maintain that pediatric antidepressants are efficacious. Discussing their research findings, they write, “[o]ur results are consistent with those reporting SSRI efficacy for major depression in children and early teens.”³⁰

These eloquent explanations, however, are not enough to convince the many Americans who see the off-label prescribing of unapproved antidepressant medications to youth as a practice with a small chance of success, but a significant risk. Joseph Barton, then-Chairman of the Committee on Energy and Commerce of the House of Representatives, for example, states, “Only one drug, Prozac, has ever been judged by the FDA to be effective for depression in children and received approval for this use. Nevertheless, I note that four different antidepressant drugs not approved for children with depression use are prescribed to children at higher rates than Prozac....”³¹ Greg Walden, Representative from the State of Oregon, expresses similar concerns,

In 2002 alone, more than 10 million American children were prescribed antidepressants, and that number is on the rise. So one has to ask, if pediatric clinical trials show that a sugar pill is about as effective as an expensive drug, is it appropriate for physicians to write millions of off-label prescriptions for kids?... Even of more concern is this: ...are physicians prescribing drugs that not only show little or no efficacy but also may show an increase in suicidal thought and action?³²

Dr. E. Jane Garland, Clinical Professor of Psychiatry and Clinical Head of the Mood and Anxiety Disorders Clinic at British Columbia’s Children’s Hospital, is even more outraged at the off-label SSRI prescriptions for children:

³⁰ Robert D. Gibbons et al., *The Relationship Between Antidepressant Prescription Rates and Rate of Early Adolescent Suicide*, 163(11) AM. J. PSYCHIATRY 1898, 1901(2006).

³¹ *Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 4 (2004) (statement of Rep. Barton, Chairman, House Comm. on Energy and Com.).

³² *Id.* at 6-7 (statement of Rep. Walden, Member, House Comm. on Energy and Com.).

In addition to their weak or nonexistent evidence of efficacy, SSRIs may have serious adverse effects in children.... up to 25% of children placed on SSRIs for any disorder will experience other psychiatric adverse effects including agitation, irritability and behavioural disinhibition.... The high placebo response of SSRIs may reinforce physician prescribing, and it has been difficult for many physicians to accept that SSRIs may be ineffective. A complicating factor is that the public at large has now accepted the model of depression as a chemical imbalance for which medication is the treatment of choice, and physicians may experience pressure to prescribe.³³

Dr. Ross Baldessarini, Professor of Psychiatry at McLean Hospital, a Harvard Medical School affiliate, and his co-authors add that “[m]ost antidepressants appear to have particularly limited beneficial effects on clinical features that may be especially relevant to suicidal risk, including agitated dysphoria, impulsivity, and aggressive tendencies, and may even worsen such features in some patients.”³⁴ These doctors wonder “why evidence of an expected protective effect of antidepressant treatment against suicide or life-threatening attempts appears to be lacking [in pediatric populations].”³⁵ They then offer a few “hypothetical possibilities” to answer this important question: that antidepressants in children may have “limited overall therapeutic effectiveness,” that “it may be difficult to document potential antisuicidal effects owing to technical limitations of available studies,” and that “[m]ixed effects, with both decreases and increases in suicidal risk may tend to cancel each other out in estimates of average trends.”³⁶

Lastly, Drs. James Leckman and Robert King, Professors in the Child Study Center and of Psychiatry at Yale Medical School, caution that “limited data suggests that the long-term use

³³ E. Jane Garland, *Facing the Evidence: Antidepressant Treatment in Children and Adolescents*, 170(4) CAN. MED. ASS’N 489, 490 (2004).

³⁴ Ross J. Baldessarini et al., *Antidepressants and Suicidal Behavior: Are We Hurting or Helping?*, 2(1) CLINICAL NEUROPSYCHIATRY 73, 74 (2005).

³⁵ *Id.*

³⁶ *Id.*

of antidepressants may be associated with the emergence of bipolar disorder and that this risk appears to be greatest among the youngest group of children exposed.”³⁷

Allegations that there exists a wide-spread practice of prescribing unsafe or ineffective medication to children are bound to raise tempers. However, the debate surrounding the off-label use of antidepressants in children is confounded by the (disputed) conclusion that these medications are associated with an increased risk of suicide ideation in pediatric populations.

Therefore, while doctors report that in their clinical experience SSRIs are both safe and effective in children, and while researchers, like Dr. Robert Gibbons et al., conduct studies that result in findings that “are consistent with those reporting SSRI efficacy for major depression in children and early teens,”³⁸ the lack of FDA approval for all of the pediatric antidepressant drugs except Prozac leaves many wary of these off-label prescriptions. Although the FDA has never said as much, it is likely that parents assume that the antidepressant medications have not been approved for use in youth specifically because of their increased risk of suicide ideation. And, with such an assumption, it is not surprising that many parents shudder at the idea of putting their children on these “deadly” antidepressant medications.

III. PEDIATRIC ANTIDEPRESSANTS & INCREASED RISK OF SUICIDALITY

The FDA decision to mandate black-box warnings for all antidepressants was based on research that, according to its interpretation, established an association between pediatric use of antidepressants and an increased risk of suicidality. In his testimony before Congress, Dr. Temple defined suicidality as suicidal thoughts and actions.³⁹ While the term suicidality can

³⁷ James F. Leckman & Robert A. King, *A Developmental Perspective on the Controversy Surrounding the Use of SSRIs to Treat Pediatric Depression*, 164(9) AM. J. PSYCHIATRY 1304, 1305 (2007).

³⁸ Robert D. Gibbons et al., *The Relationship Between Antidepressant Prescription Rates and Rate of Early Adolescent Suicide*, 163(11) AM. J. PSYCHIATRY 1898, 1901(2006).

³⁹ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on*

include, as part of its definition, completed suicides, because there were no completed suicides in the studies that were reviewed by the FDA,⁴⁰ for the purposes of this paper, suicidality refers only to suicidal ideation and nonfatal suicide attempts. However, even with this definitional restriction, a number of scholars who specialize in this area have called into question the FDA's conclusion that the research suggests a link between pediatric antidepressant use and an increased risk of suicidality. Before discussing the actions taken by the FDA in response to the research with which it was presented, and before evaluating the closeness of fit between the perceived problem of increased risk of suicidality and the FDA's solution, both sides of the debate on pediatric antidepressant use and increased risk of suicidality must be presented.

Dr. Temple explains why the correct interpretation of the research in this area is of such significant consequence:

Whether anti-depressant drug use causes suicidal thinking or behavior in pediatric patients (or adults) is a critically important question that we must answer in a careful, thoughtful manner. A premature conclusion or emphasis in either direction could have adverse consequence for those who are suffering from depression. Missing or understating a signal of increased risk of suicidality could result in greater reassurance than is warranted about the safety of these drugs, insufficient attention to the patients being treated, and perhaps too casual use of the drugs. On the other hand, overstating the risk could result in overly conservative use of these drugs or excluding their use for the pediatric population, and inadequate treatment of a potentially fatal condition.⁴¹

Energy and Com., 108th Cong. 78 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

⁴⁰ U.S. FOOD & DRUG ADMIN., REPORTS OF SUICIDALITY IN PEDIATRIC PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS FOR MAJOR DEPRESSIVE DISORDER (MDD) (OCTOBER 27, 2003).

⁴¹ *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 70 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

A. FDA INTERPRETATION OF DATA AS INDICATING INCREASED RISK OF SUICIDALITY: THOSE IN FAVOR

Dr. Thomas Newman, Professor of Epidemiology, Biostatistics, and Pediatrics at the University of California, San Francisco, who “strongly favored the black box warning,” describes the process through which the FDA data was obtained:

During consideration of the proposed labeling change, the committee heard a number of presentations summarizing evidence that suicidality in children and adolescents may be increased by the newer antidepressant drugs, primarily selective serotonin-reuptake inhibitors. The most convincing evidence came from an FDA analysis of randomized trials. Most of these trials had been conducted by the drug manufacturers under the Best Pharmaceuticals for Children Act, which provides companies an additional six months patent protection for their product if they do pediatric studies. These studies need not be published and need not be of high quality. In fact, we heard that because these medications are already widely prescribed ‘off-label’ and patents may be close to expiration, sponsors may have more incentive to do the studies quickly than to do them well. To facilitate analysis of the patchwork of pediatric studies, the FDA obtained narratives of adverse-event reports from the trials and contracted with the experts on suicide at Columbia University to review them. The Columbia staff members, who were unaware of the treatment-group assignments, were asked to determine whether the adverse events represented suicidality. FDA staff members then combined the results into a meta-analysis.⁴²

According to a medical news source, the findings were

derived from a pooled analysis of data from 319 short-term placebo-controlled antidepressant drug trials.... Drug trials included the analysis of 24 short-term (median duration, 2 months) pediatric and adolescent studies of 9 antidepressant medications (n>4400) and 295 studies of 11 antidepressant agents in more than 77,000 adult patients with MDD and other psychiatric disorders.⁴³

On September 13th and 14th, 2004, Dr. Tarek Hammad, Senior Medical Reviewer for the Division of Neuropharmacological Drug Products in the Center for Drug Evaluation and

⁴² Thomas B. Newman, *A Black-Box Warning for Antidepressants in Children?*, 351(16) NEW ENGL. J. MED. 1595, 1596 (2004).

⁴³ Yael Waknine, *FDA Safety Changes: Antidepressants and Tykerb*, MEDSCAPE MED. NEWS, Nov. 28, 2007, <http://www.medscape.org/viewarticle/566556> (last visited January 20, 2011).

Research at the FDA, presented the findings from the meta-analysis to the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee at the FDA.⁴⁴

An article released by a medical news source reported that the meta-analysis revealed that “[a]n increase of 5 additional [suicidality] cases per 1000 patients occurred in young adults aged 18 to 24 years, which was lower than that observed among pediatric patients aged younger than 18 years (14 additional cases per 1000 patients).”⁴⁵ To this, Dr. Newman adds his scholarly interpretation of the results,

[w]hen all the pediatric trials were pooled, the rate of definite or possible suicidality among children assigned to receive antidepressants was twice that in the placebo group.... Although the FDA staff did not provide this information to the committee, according to [Dr. Newman’s] calculations, such a dramatic result would be expected to occur by chance only 1 time in 20,000 ($P=0.00005$).⁴⁶

Next, Dr. Newman outlines some limitations of the meta-analysis, including the “relatively small number of events,” the fact that the “trials had not been designed to evaluate suicidality,” and the non-uniformity of the “methods of ascertainment and classification of the events in the various trials” but notes that in his opinion, “these concerns only made the results more compelling.”⁴⁷ He explains that,

[i]nadequate sample size and misclassification of outcomes make it more – not less – difficult to detect differences between groups in randomized, blinded trials. The fact that an association emerged from the meta-analysis with a P value of 0.00005, for an outcome that the sponsors of the trials were not looking for, and presumably did not wish to find, was quite convincing.⁴⁸

Dr. Newman also details the

⁴⁴ Tarek A. Hammad, *Results of the Analysis of Suicidality in Pediatric Trials of Newer Antidepressants*, Microsoft PowerPoint Presentation for Psychopharmacologic Drugs Advisory Comm. and the Pediatric Advisory Comm. of the U.S. Food & Drug Admin. (September 13-14, 2004) (available at www.fda.gov/ohrms/dockets/ac/04/.../2004-4065S1_08_FDA-Hammad.ppt, last visited January 20, 2011).

⁴⁵ Yael Waknine, *FDA Safety Changes: Antidepressants and Tykerb*, MEDSCAPE MED. NEWS, Nov. 28, 2007, <http://www.medscape.org/viewarticle/566556> (last visited January 20, 2011).

⁴⁶ Thomas B. Newman, *A Black-Box Warning for Antidepressants in Children?*, 351(16) NEW ENGL. J. MED. 1595, 1596 (2004).

⁴⁷ *Id.*

⁴⁸ *Id.*

public testimony from people who believed that antidepressant drugs had caused their loved ones to commit suicide.... Several of these cases involved patients who had shown no hint of suicidality before beginning treatment with the drugs and who had been given these drugs for indications other than depression, including migraine headaches, nail biting, anxiety, and insomnia.⁴⁹

Dr. Newman confirms that “[t]he FDA’s meta-analysis suggested that the new antidepressants double the risk of suicidality, from about 2.5 percent to 5 percent, in trials lasting two or three months,” and from this, concludes that these findings provide strong support for the FDA’s decision to require a black-box warning.⁵⁰ Dr. Temple, of the FDA, supports this interpretation of the data, stating, “the analysis showed that, as a group, the antidepressants studied, both SSRIs and the so called atypical, increased the risk of suicidality. There was variation from drug to drug and variation from study to study, but the roughly twofold increased risk was reasonably consistent across drugs.”⁵¹ Dr. Temple adds that, “the combined Pediatric and Psychopharm Drugs Advisory Committees agreed with FDA’s conclusions that the data in aggregate indicated an increased risk of suicidality in pediatric patients....”⁵² Dr. Baldessarini et al. also agree with the conclusion that there is evidence to support an association between pediatric antidepressant use and an increased risk of suicidality. They write,

Suicide attempt-rates in children and adolescents are not well established, but can be estimated at 10-20-times the suicide rate... in the general population. Among juveniles with depressive or anxiety disorder in [S]SRI trials, the suicide-attempt rate... was 50-times greater, despite efforts to exclude suicidal subjects from most trials. The pooled *relative risk* (RR) for attempts during treatment of juveniles randomized to [S]SRI vs. placebo was 1.90..., despite a wide range across trials..., supporting recent regulatory cautions about the use of [S]SRIs in children and adolescents....⁵³

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 66 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

⁵² *Id.* at 66-67.

⁵³ Ross J. Baldessarini et al., *Antidepressants and Suicidal Behavior: Are We Hurting or Helping?*, 2(1) CLINICAL NEUROPSYCHIATRY 73, 73 (2005).

Dr. Bridge et al. offer more qualified support for the FDA's position. They state, "Consistent with the analyses of the FDA, we found evidence of an overall small but increased risk of treatment-emergent suicidal ideation/suicide attempt. However, the pooled random-effects risk differences of suicidal ideation/suicide attempt for each indication were all less than 1%."⁵⁴

Furthermore, Dr. Hammad warns critics not to take comfort in the fact that there were no actual suicides in the analyzed studies. He writes, "[T]he finding of no completed suicides among the approximately 4600 patients in the 24 trials evaluated does not provide much reassurance regarding a small increase in the risk of suicide because this sample is not large enough to detect such an effect."⁵⁵

B. FDA INTERPRETATION OF DATA AS INDICATING INCREASED RISK OF SUICIDALITY: THOSE AGAINST

Despite these strong assertions that the data supports a finding of increased risk of suicidality, many scholars disagree with this interpretation and argue that, at worst, the data is inconclusive, and at best, the data supports the exact opposite conclusion. Even Dr. Temple concedes,

[i]t might be possible to demonstrate that anti-depressants cause an increase in suicidality through randomized clinical trials, but these trials would need to be quite large because suicidality is not common. It might be possible to pool results of many trials, but if this involves results from studies of different drugs, the question remains whether some drugs could behave differently from others. Furthermore, assessing this risk in uncontrolled data is particularly difficult because depression itself causes suicidality. In any given case, one cannot usually distinguish whether the suicidality occurred because of the drug or despite it.⁵⁶

⁵⁴ Jeffrey A. Bridge et al., *Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials*, 297(15) J. AMER. MED. ASS'N 1683, 1692 (2007).

⁵⁵ Tarek A. Hammad et al., *Suicidality in Pediatric Patients Treated With Antidepressant Drugs*, 63 ARCHIVES GEN. PSYCHIATRY 332, 338 (2006).

⁵⁶ *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 69 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

The distinction between symptom and side effect is an especially difficult one to draw when the study findings seem to support polar-opposite conclusions. David Brent, Professor of Psychiatry specializing in adolescent behavior and suicidal behavior at the Western Psychiatric Institute and Clinic at the University of Pittsburgh Medical Center, states that, “the same FDA analyses that showed an increase in the risk for spontaneously reported suicidal events associated with antidepressants showed a tendency toward a *protective* effect against new-onset and worsening suicidal ideation in the subset of trials for which suicidal ideation was assessed systematically”(emphasis original).⁵⁷

Also arguing in favor of inconclusiveness, say the critics, are the many study limitations. Dr. Gregory Simon, a psychiatrist at the Group Health Research Institute, is one of many who cautions that the results of the FDA meta-analysis should not be accepted as final. He states, “[a] randomized trial to definitely determine whether a specific antidepressant increases or decreases risk of suicide death would need to include several hundred thousand patients. Such a study will never occur.”⁵⁸ Dr. Simon continues to counter the FDA findings with a discussion of several study limitations of the meta-analysis:

Using data from all placebo-controlled antidepressant trials in children and adolescents, Hammad and colleagues at the U.S. Food and Drug Administration (FDA) found that risk of suicidal ideation and suicidal behavior was nearly twice as high during treatment with several newer antidepressants compared with placebo. It is important to note that the number of actual suicide attempts in those placebo-controlled trials was too small to compare and that the number of suicide deaths was zero....[Additionally,] [r]ecent evidence suggests that effects on suicidality may differ across antidepressants. In the FDA meta-analysis of pediatric trials, risk ratios comparing individual drugs to placebo ranged from 1.4 to 5.5. Venlafaxine was the only individual drug for which the increase in risk was statistically significant.⁵⁹

⁵⁷ David Brent, *Antidepressants and Suicidal Behavior: Cause or Cure?*, 164(7) AM. J. PSYCHIATRY 989, 989 (2007).

⁵⁸ Gregory E. Simon, *How Can We Know Whether Antidepressants Increase Suicide Risk?*, 163(11) AM. J. PSYCHIATRY 1861, 1861 (2006).

⁵⁹ *Id.*

Dr. Gibbons et al. emphasize Dr. Simon's first point, stating,

[S]ince no completed suicides were reported in any of these studies, their analysis was based exclusively on nonfatal suicide attempts and suicidal ideation. Attempts and ideation are common in adolescents and children, are often not reported to adults, and serve only as a surrogate measure of suicide.⁶⁰

Moreover, Dr. Wheadon draws attention to the fact that the classification system for suicide-related adverse events may have over-stated the risk. He explains,

[E]valuation of safety and tolerability is confounded by the fact that the cardinal symptoms of the disease such as anxiety, sleep disturbance and suicidality may masquerade as side-effects of treatment. It is precisely for this reason that the symptom complex of suicidal thinking, suicide attempts, and completed suicides – which we refer to as suicidality – is particularly difficult to assess in antidepressant clinical trials.... GSK's [GlaxoSmithKline] meta-analysis of the pediatric clinical trial data... utilized an algorithm approach, evaluating adverse event reports and classifying them as "possibly suicide-related" and/or "suicide attempt." This could be imprecise; for example, one classification of suicidality in one of our trials consisted of a subject slapping her face.⁶¹

David Gunnell, Ph.D., Professor of Epidemiology at the University of Bristol, and Deborah Ashby, Professor of Medical Statistics and Co-Director of the Imperial Clinical Trials Unit at the Imperial College of London, raise a concern about the short duration of the studies and the lack of follow-up to determine the long-term benefits of antidepressant use. They write,

[C]urrent concerns about the safety of SSRIs come from clinical trials both of too short duration (<10 weeks) to identify longer term beneficial effects and are carried out in children and adolescents, among which suicide is rare.⁶²...[A]ny increased risk may be counterbalanced by a longer term reduction in suicidal behavior; such benefits would not [be] detected in the trials as they generally lasted 10 weeks or less, whereas the mean duration of treatment in clinical practice is three to four months.⁶³

Dr. Brent calls attention to another type of study limitation. He explains,

⁶⁰ Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164(9) AM. J. PSYCHIATRY 1356, 1360 (2007).

⁶¹ *Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 53 (2004) (statement of Dr. David E. Wheadon, Senior Vice President of U.S. Regulatory Affairs at GlaxoSmithKline).

⁶² David Gunnell & Deborah Ashby, *Antidepressants and Suicide: What is the Balance of Benefit and Harm*, 329 BRIT. MED. J. 34, 37 (2004).

⁶³ *Id.* at 35-36.

One difficulty that cannot be overcome... is that only *spontaneously reported* adverse events were available for classification. It is unclear if what is being measured is the impact of medication on the *threshold* for spontaneous reporting between treatments or on *actual* suicidal ideation and behavior.⁶⁴

Dr. Hammad concedes this as well. He states,

[T]he apparent increased risk of drug-induced suicidality may actually represent a greater likelihood of reporting of suicidality events by patients rather than an increased rate of the events themselves....⁶⁵

And, to explain why there might be an increase in reporting, Dr. Gunnell and Ms. Ashby propose a theory of disinhibition.⁶⁶ They write, “Interpretation of this apparent increase in risk is problematic as people taking SSRIs may be more likely to report adverse effects, perhaps because the drugs could have a disinhibiting effect.”⁶⁷ Dr. Fassler adds,

It does appear that these medications may increase the likelihood that a patient will actually tell someone about their suicidal thoughts or even about a suicide attempt. From my perspective, as a child and adolescent psychiatrist, this is actually a good thing, because it means you have the opportunity to intervene and to keep the person safe. I believe this is why none of the studies have demonstrated any increase in actual deaths from suicide in conjunction with the use of these medications.⁶⁸

Dr. Gibbons et al. stress the point regarding the greater likelihood of reporting. They then list two additional methodological limitations of the FDA’s meta-analysis “that could affect its conclusions.”⁶⁹ They state that

[b]ecause active medications generally have more side effects than placebo, the active treatment group will typically have more expansive medical records as a result of greater

⁶⁴ David Brent, *Antidepressants and Suicidal Behavior: Cause or Cure?*, 164(7) AM. J. PSYCHIATRY 989, 989 (2007).

⁶⁵ Tarek A. Hammad et al., *Suicidality in Pediatric Patients Treated With Antidepressant Drugs*, 63 ARCHIVES GEN. PSYCHIATRY 332, 338 (2006).

⁶⁶ David Gunnell & Deborah Ashby, *Antidepressants and Suicide: What is the Balance of Benefit and Harm*, 329 BRIT. MED. J. 34, 35-36 (2004).

⁶⁷ *Id.*

⁶⁸ *FDA’s Drug Approval Process: Up to the Challenge?: Hearing Before the Comm. on Health, Educ., Lab., and Pensions*, 109th Cong. 44 (2005) (statement of Dr. David Fassler, Board certified child and adolescent psychiatrist, member of the Board of Trustees for the American Psychiatric Association (APA), Clinical Associate Professor of Psychiatry at the University of Vermont).

⁶⁹ Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators’ Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164(9) AM. J. PSYCHIATRY 1356, 1360 (2007).

contact with the treatment team and therefore a greater likelihood of reporting suicide ideation or behavior.... A...possible ascertainment bias applies to suicide attempts by overdose of study medication, which may go undetected in patients on placebo, whereas among those on active medication, more cases of medication overdose will be symptomatic and result in contact with health care staff in an emergency department or study staff. This ascertainment bias can result in underreporting of suicide attempts in placebo groups and make it appear as if antidepressant treatment were related to a higher rate of suicide attempt....

Second, by design, the randomized controlled trials analyzed by the FDA systematically excluded patients who were actively suicidal, and thus the FDA lacks data on those who are at highest risk of suicide. Third, the FDA's analysis of the only systematic and prospectively collected suicidality measure... revealed no association with treatment.⁷⁰

Similarly, Dr. Hammad suggests,

It is also possible that patients assigned to active drug therapy in these trials may have had other adverse events that drew clinical attention to them and resulted in better ascertainment for suicidality.⁷¹

Even assuming *arguendo* that pediatric antidepressant use is associated with an increased risk of suicidality, Dr. Gunnell and Ms. Ashby offer an alternative explanation for the data: that an increase in suicidality may not be medicine specific, but common to all effective treatments. They state, “[R]esponse to treatment may lead to reactivation among people whose depression previously prevented them from acting on suicidal impulses.”⁷² Dr. Martin Teicher, Psychiatrist and Director of the Developmental Biopsychiatry Research Program and Laboratory of Developmental Psychopharmacology at McLean Hospital, a Harvard Medical School affiliate, supports the conclusion that reactivation may play a role in any increase of suicidality. Dr. Teicher calls this the “Roll back phenomenon.”⁷³ He writes, “[A]nti-depressants with prominent

⁷⁰ *Id.* at 1360-61.

⁷¹ Tarek A. Hammad et al., *Suicidality in Pediatric Patients Treated With Antidepressant Drugs*, 63 ARCHIVES GEN. PSYCHIATRY 332, 338 (2006).

⁷² David Gunnell & Deborah Ashby, *Antidepressants and Suicide: What is the Balance of Benefit and Harm*, 329 BRIT. MED. J. 34, 35 (2004).

⁷³ *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on*

energizing effects might actually increase suicidal behavior in severely depressed patients who are suicidal but also have psychomotor retardation and are thus inhibited from acting on their suicidal thoughts.”⁷⁴ Dr. Wheadon explains why this might be the case. He states, “[D]uring early treatment and recovery, symptom such as lack of energy and motivation may improve ahead of depressive and suicidal thinking. The possible consequence of this is that these still-depressed patients may now have the energy and motivation to act on their suicidal thoughts.”⁷⁵

C. ADDITIONAL EVIDENCE: FINDINGS FROM OTHER RESEARCH STUDIES AND ANALYSES OF SUICIDE RATE TRENDS

The aforementioned challenges to the FDA conclusion of increased risk of suicidality have revolved around study limitations of, and the alternative explanations for the findings from, the FDA meta-analysis. However, scholars have also used evidence of recent suicide trends as well as their own research findings in order to dispute the FDA’s interpretation.

For example, based on an analysis of 65,103 patients with 82,285 episodes of antidepressant treatment, Dr. Gregory Simon et al. concluded that the “data do[es] not suggest increased risk of suicide death or serious suicide attempt during the first month of antidepressant treatment....suicide deaths appeared relatively constant over the first 6 months of treatment.”⁷⁶ Additionally, Dr. Simon et al. found “no evidence of greater risk for the newer drugs included in the FDA advisory. Overall risk did not differ by drug class after adjustment for year of treatment. The results of the month-by-month comparison of newer and older drugs certainly

Energy and Com., 108th Cong. 69 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

⁷⁴ *Id.*

⁷⁵ *Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 54 (2004) (statement of Dr. David E. Wheadon, Senior Vice President of U.S. Regulatory Affairs at GlaxoSmithKline).

⁷⁶ Gregory E. Simon et al., *Suicide Risk During Antidepressant Treatment*, 163(1) AM. J. PSYCHIATRY 41, 43-45 (2006).

argue against any increase in risk specific to newer antidepressants.”⁷⁷ Perhaps even more persuasive, these researchers found that “[t]he peak period of attempts was in the month *before* the initiation of treatment, regardless of the setting or type of treatment.”⁷⁸ Dr. Simon along with his co-author, James Savarino, Ph.D., then-Research Programmer at Group Health Research Institute, add the findings from a related study:

We found the same pattern in the timing of suicide attempts among patients starting depression treatment with psychotherapy as among those starting antidepressant medication, either from a primary care physician or a psychiatrist. In all three groups, the incidence of suicide attempt was highest in the month before the start of treatment and declined steadily over the next 6 months.... Although the incidence was higher in the first month of treatment than in subsequent months, this should not be attributed to a specific adverse effect of medication.⁷⁹

As a result, Drs. Simon and Savarino stress the “need to consider the previous history of suicidal behavior and its role in referral when evaluating the relationship between treatment and subsequent behavior.”⁸⁰ They also emphasize that any increase in suicidality is not medicine-specific and should not be attributed to the pediatric use of antidepressants. It is important to note that Dr. Simon’s studies involved participants of all ages, not only children, adolescents, and young adults; however, the findings were consistent across all age ranges.

Even Dr. Hammad, upon whose analysis the FDA relied in making its determination regarding the black-box warnings, admits that

there are other pertinent data that seem inconsistent with a role for antidepressant drugs in inducing suicidality in pediatric patients. The absolute rate of adolescent suicide in the United States has declined in recent years... There are ecologic data suggesting that increasing prescriptions for antidepressant drugs in adolescents are associated with a decrease in adolescent suicide. In addition, 2 recent autopsy studies have failed to find

⁷⁷ *Id.* at 45.

⁷⁸ David Brent, *Antidepressants and Suicidal Behavior: Cause or Cure?*, 164(7) AM. J. PSYCHIATRY 989, 989 (2007).

⁷⁹ Gregory E. Simon & James Savarino, *Suicide Attempts Among Patients Starting Depression Treatment With Medications or Psychotherapy*, 164(7) AM. J. PSYCHIATRY 1029, 1031-32 (2007).

⁸⁰ David Brent, *Antidepressants and Suicidal Behavior: Cause or Cure?*, 164(7) AM. J. PSYCHIATRY 989, 989 (2007).

evidence of antidepressant drug use in most adolescent victims, even in those who had been prescribed antidepressants before their death.⁸¹

Dr. Hammad's first point is one that is made by many scholars in this area. Dr. Gunnell and Ms. Ashby, for instance, cite statistics that "in the United States, ... areas with the largest increases in antidepressant prescribing to 10-19 year olds experienced the greatest fall in suicide."⁸² Additionally, a study published in the Archives of General Psychiatry found that "for each 1 percent increase in the use of SSRIs among adolescents, there was a decrease of 0.23 suicides per 100,000 adolescents per year."⁸³ Furthermore, Dr. Fassler, discussing suicide rates prior to 2005, writes "the adolescent suicide rate in the country has actually declined by over 25 percent since the early 1990's, in a manner consistent with the increased use of SSRI antidepressants."⁸⁴ Dr. Gibbons et al. documented the inverse relationship between rate of antidepressant use and rate of suicidality in their work as well. According to their findings, "[a]ll of the treatment groups, regardless of the type of antidepressant prescribed, showed large decreases in the rate of suicide attempts after initiation of treatment. ... In addition, ... the rates of suicide attempts in patients treated with an antidepressant were roughly one-third of those observed for patients who were not treated with an antidepressant."⁸⁵ Researchers caution that such findings do not prove that antidepressant treatment reduces suicidal behavior, they do

⁸¹ Tarek A. Hammad et al., *Suicidality in Pediatric Patients Treated With Antidepressant Drugs*, 63 ARCHIVES GEN. PSYCHIATRY 332, 338 (2006).

⁸² David Gunnell & Deborah Ashby, *Antidepressants and Suicide: What is the Balance of Benefit and Harm*, 329 BRIT. MED. J. 34, 36 (2004).

⁸³ *Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 53 (2004) (statement of Dr. David E. Wheadon, Senior Vice President of U.S. Regulatory Affairs at GlaxoSmithKline).

⁸⁴ *FDA's Drug Approval Process: Up to the Challenge?: Hearing Before the Comm. on Health, Educ., Lab., and Pensions*, 109th Cong. 44 (2005) (statement of Dr. David Fassler, Board certified child and adolescent psychiatrist, member of the Board of Trustees for the American Psychiatric Association (APA), Clinical Associate Professor of Psychiatry at the University of Vermont).

⁸⁵ David Brent, *Antidepressants and Suicidal Behavior: Cause or Cure?*, 164(7) AM. J. PSYCHIATRY 989, 990 (2007).

“strongly support the converse conclusion: *it is much more likely that suicidal behavior leads to treatment than that treatment leads to suicidal behavior*” (emphasis original).⁸⁶

Dr. Hammad’s second point, regarding adolescent autopsy results, is also supported by a number of the researchers who specialize in the analysis of adolescent suicidality. Dr. Gibbons et al., for example, write,

The FDA’s findings for children appear to be inconsistent with psychological autopsy studies of suicide victims suggesting that few pediatric suicide victims have been exposed to SSRIs and with ecological studies on completed suicide attempts that indicate a protective effect of SSRIs in children and adolescents.⁸⁷

They also note that,

Most depressed people who eventually commit suicide seek professional help within 1 month before death. However, most are not on antidepressant medications at the time of death, which suggests that lack of treatment contributes to suicide risk and that more widespread antidepressant treatment might reduce suicide rates.⁸⁸

In sum, the FDA itself, in an article on its website, acknowledges that “while some adolescents may demonstrate a worsening of suicide ideation, up to 40-60% will demonstrate an improvement in suicidal ideation and similar proportions will demonstrate a meaningful reduction in other symptoms of depression.”⁸⁹ Dr. Gibbons expresses this message in a stronger form. He declares, “studies clearly show that the greatest risk of suicide is depression... Failure to treat depression, either using pharmacotherapy or psychotherapy, will lead to dramatic increases in the rate of serious suicide attempts and completions in the U.S. and in the world.”⁹⁰

⁸⁶ *Id.*

⁸⁷ Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators’ Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164(9) AM. J. PSYCHIATRY 1356, 1357 (2007).

⁸⁸ *Id.* at 1356.

⁸⁹ U.S. FOOD & DRUG ADMIN., ACNP COMMENTS ON SSRI USE IN ADOLESCENTS 1, 5 (2004).

⁹⁰ Nicholas Bakalar, *Suicide Findings Question Link to Antidepressants*, N.Y. TIMES, July 10, 2007, <http://www.nytimes.com/2007/07/10/health/psychology/10depre.html> (last visited January 20, 2011).

D. MITIGATING FACTORS

In addition to arguing against the FDA's conclusion of increased risk of pediatric suicidality, critics are quick to offer evidence of mitigating factors that temper the FDA's findings and serve to soothe some of the fears associated with pediatric antidepressant use.

As an initial matter, the critics stress that suicidality rarely occurs randomly or suddenly. Researchers have not found support for Dr. Newman's aforementioned anecdotes in which family members fervently asserted that their loved ones, "who had shown no hint of suicidality before beginning treatment with the drugs and who had been given these drugs for indications other than depression....,"⁹¹ suddenly committed suicide because of antidepressant use. Dr. Baldessarini et al. write, "It is important to emphasize that suicidality newly emerging during antidepressant treatment seems rarely to arise without warning, provided that patients are adequately monitored."⁹²

Next, critics identify the "warning signs" that often precede suicidality. Dr. Baldessarini et al. explain that "in [their] trials, suicidality was much more frequent with newly emerging anger or agitation...."⁹³ In line with this, Dr. Bridge et al. have found that symptoms at intake may affect the risk of suicidality. They state, "self-reported suicidal ideation and irritability at intake have been found to predict future suicidal ideation/suicide attempt."⁹⁴ Mental health professionals, therefore, should pay special attention to those presenting with self-reported suicidal ideation and irritability, and should monitor all patients closely for signs of newly-emerging anger or

⁹¹ Thomas B. Newman, *A Black-Box Warning for Antidepressants in Children?*, 351(16) NEW ENGL. J. MED. 1595, 1596 (2004).

⁹² Ross J. Baldessarini et al., *Antidepressants and Suicidal Behavior: Are We Hurting or Helping?*, 2(1) CLINICAL NEUROPSYCHIATRY 73, 74 (2005).

⁹³ *Id.* at 73.

⁹⁴ Jeffrey A. Bridge et al., *Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials*, 297(15) J. AMER. MED. ASS'N 1683, 1694 (2007).

agitation. Because it may be impracticable for health care providers to offer frequent and thorough evaluations to all of their pediatric patients who are taking antidepressants, it is important to identify the most vulnerable subset of that population and focus the attention on those individuals; the recognition of certain “warning signs” of suicidality will allow us to do just that. Even if there is an increased risk of suicidality associated with pediatric use of antidepressants, knowing the “warning signs” and acting to protect the patients who display them, will allow us to mitigate the potential medication risks.

IV. FDA RESPONSE

The debate over the interpretation of the data quickly entered the world of public policy. Susan Busch, Ph.D., Associate Professor of Public Health and Director of the Health Management Program at the Yale School of Public Health, et al. clarify the respective positions of the proponents and the opponents of the action undertaken by the FDA in response to the study findings. They write,

[s]upporters of the FDA’s actions argued that the evidence of elevated risks of suicidality linked to use of antidepressants by youth was sufficiently serious to warrant informing providers and consumers. Critics countered that such action would significantly reduce the use of an effective treatment for depression, thereby producing poorer mental health outcomes (including possibly increased risk of suicide) in an underserved population.⁹⁵

Concern about pediatric antidepressant use began in 2003, when “in [his] review of the Paxil pediatric supplement, [Andrew Mosholder, Medical Officer for the Office of Drug Safety of the FDA,] noted that a number of clinical trial adverse events designated as ‘emotional lability’ involved suicidal behavior or ideation.”⁹⁶ It is worth noting that the year 2003 was long before

⁹⁵ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11, 11 (2010).

⁹⁶ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 23 (2004) (statement of Dr. Andrew D. Mosholder, Medical Officer in the Office of Drug Safety at the FDA).

the meta-analysis findings were released, and in fact, before the meta-analysis studies were even commissioned. According to the FDA, the adverse events in the Paxil study provided the first indication of increased risk of suicidality associated with pediatric antidepressant use.

In response to preliminary findings from the Paxil trials, the FDA issued “[a] request for a more focused analysis of the Paxil suicidality data [which in turn] led to a further suggestion of an increased rate of suicidality in the Paxil treated patients....”⁹⁷ As a result, on June 19, 2003, the FDA released a Public Health Advisory recommending against the use of Paxil as a pediatric antidepressant.⁹⁸ More specifically, the FDA “describ[ed] the results of the Paxil evaluation and stat[ed] that, although FDA had not completed its evaluation, [it] recommended that Paxil not be used in children and adolescents to treat major depressive disorder.” Moreover, in this safety warning, the FDA raised questions about the efficacy of Paxil (generic form: paroxetine) in the pediatric population. The FDA wrote that

‘three well-controlled trials in pediatric patients with MDD failed to show that the drug was more effective than placebo..., [that there was] no evidence that Paxil is effective in children or adolescents with major depressive disorder..., [and that Paxil was] not currently approved for use in children and adolescents.’⁹⁹

To emphasize, the June 2003 FDA warning regarding the pediatric use of antidepressants focused exclusively on Paxil and in no way implicated the broader category of SSRIs.¹⁰⁰

Despite the extensive review of the preliminary data, both by the FDA, and by outside experts at Columbia University, the results remained inconclusive.¹⁰¹ Therefore, on October 3,

⁹⁷ *Id.* at 65 (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

⁹⁸ *Id.*

⁹⁹ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11,12 (2010).

¹⁰⁰ *Id.*

¹⁰¹ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 75 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

2003, the FDA “requested patient-level data sets from [the drug] manufacturers.”¹⁰² Under the Food and Drug Administration Modernization Act, and more specifically, the Best Pharmaceuticals for Children Act of 2002, the drug companies were provided six months of additional patent protection for conducting the requested pediatric antidepressant studies.¹⁰³ Collectively, the data from these FDA-commissioned drug-manufacturer studies would become the basis for the oft-referred-to “meta-analysis.”

On October 27, 2003, the FDA issued a letter to health care professionals entitled, “Reports of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD).”¹⁰⁴ In the letter, the FDA wrote that, “a preliminary review of...reports for 8 antidepressant drugs (citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine),” resulted in data suggesting “an excess of ... reports [of suicidality] for patients assigned to several of these antidepressant drugs compared to those assigned to placebo.”¹⁰⁵ Although the FDA expressly stated that, “[i]n the 20 placebo-controlled trials being considered for these 8 drugs, involving over 4100 pediatric patients, there have been no reports of completed suicides,” the FDA concluded its letter with the text of the warning found on antidepressant labeling and the following boldfaced sentence: “**FDA emphasizes that these drugs must be used with caution**” (emphasis original).¹⁰⁶ In addition to the information regarding suicidality, the FDA announced that “data reviewed by FDA were adequate to establish effectiveness in MDD for only one of these [eight] drugs, Prozac (fluoxetine)” and the FDA recommended “close supervision of high-risk patients” as an

¹⁰² *Id.*

¹⁰³ *Id.* at 64.

¹⁰⁴ U.S. FOOD & DRUG ADMIN., REPORTS OF SUICIDALITY IN PEDIATRIC PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS FOR MAJOR DEPRESSIVE DISORDER (MDD) (OCTOBER 27, 2003).

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

accompaniment to initial drug therapy.¹⁰⁷ According to researchers, the statement that Prozac, and Prozac alone, met FDA standards for safety and efficacy in children, and the recommendation of close supervision for patients beginning an antidepressant regimen were “two new pieces of information” from the FDA.¹⁰⁸

According to Dr. Temple, during the February 2, 2004 Advisory Committee Meeting, “some in the agency” made clear that they “thought the results [of the studies] were, in fact, definitive and could be a basis for a change in labeling to discourage use of the [antidepressant] drug[s], except for Prozac, in children.”¹⁰⁹ Moreover, the Committee “recognized that whatever the relationship of anti-depressants to suicidality, it was perfectly clear even then that the period after initiation of treatment for depression was of great concern and that physicians needed to be warned about this, the need to be careful and make close observations.”¹¹⁰ Consequently, on March 22, 2004 the FDA took its third public action, requiring “manufacturers... to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients treated with [the relevant antidepressant medications] for worsening depression or the emergence of suicidality.”¹¹¹ Ten drugs were to include this warning on their products. They were: Prozac (fluoxetine); Zoloft (sertraline); Paxil (paroxetine); Luvox (fluvoxamine); Celexa (citalopram); Lexapro (escitalopram); Wellbutrin (bupropion); Effexor (venlafaxine); Serzone (nefazodone); and Remeron (mirtazapine).¹¹² This advisory also underlined some of the

¹⁰⁷ *Id.*

¹⁰⁸ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11,12 (2010).

¹⁰⁹ *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 66 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

¹¹⁰ *Id.*

¹¹¹ U.S. FOOD & DRUG ADMIN., *WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANTS* (MARCH 22, 2004).

¹¹² *Id.*

statements made in the October 2003 letter by reiterating the “information on the efficacy of fluoxetine in treating children and more explicitly emphasiz[ng] the importance of monitoring.”¹¹³

By fall of 2004, the results from the FDA-commissioned drug-manufacturer studies had been submitted to the FDA and rigorously analyzed. On September 13, 2004, Dr. Hammad presented the findings from the meta-analysis to the Psychopharmacological Drugs and Pediatric Advisory Committees.¹¹⁴ The Advisory Committees

agreed with the FDA’s conclusions that the data in aggregate indicated an increased risk of suicidality in pediatric patients and made several critical recommendations. First, they believed the conclusion should apply to all of the studied drugs, even though it was more prominent in some than others. They also strongly urged that we apply it to any new anti-depressant and to the older anti-depressants, including the tricyclics...partly because the logic seemed to be that this [increased risk of suicidality] is a property of anti-depressants.... They did not believe the anti-depressants, other than fluoxetine, should be contraindicated in children... and two-thirds of them thought the new warning information should be boxed.¹¹⁵

The committee members voted 15-8 to recommend that a black-box warning describing the increased risk of suicidality be included on the labeling for all antidepressant medications.¹¹⁶

Dr. Curtis Rosebraugh, Director of Drug Evaluation II in the Center for Drug Evaluation and Research at the FDA, explains the difference between a black-box warning and a cautionary statement made in the warnings section of the prescription label. He states,

A boxed warning is used in situations to highlight information that is the in warning section of the label that is especially important to prescribers.... We have several criteria that we use when evaluating whether something should be in a boxed warning instead of in the warning section. And I think the one that applies here is that there is a serious adverse reaction that

¹¹³ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11,12 (2010).

¹¹⁴ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 66 (2004) (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

¹¹⁵ *Id.* at 66-67.

¹¹⁶ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11,12 (2010).

can be prevented or perhaps reduced in frequency or severity by appropriate use of the drug which would include careful monitoring.¹¹⁷

However, the added attention to the warning that results from its being boxed may also dissuade some patients from using the medication altogether. Dr. Temple acknowledges this when he states,

We have been trying to get the entire world to stop calling these things black boxes and to call them what they're supposed to be called, boxed warnings, because black box carries the implication don't you dare use this and that is absolutely not the intent of this boxed warning.¹¹⁸

In addition to possibly discouraging the use of the drug through the strength of the box warning, the box warning also affects the ability of the manufacturers to advertise the product. Dr. Rosebraugh adds, "They [drug manufacturers] can continue to advertise...with one caveat: they can't do reminder ads.... [R]eminder ads are where they don't specifically mention the drug but they talk about the disease. They can no longer do that if they have a boxed warning."¹¹⁹

Therefore, a black-box warning can potentially hurt manufacturers both through a reduction in prescriptions based on patient fear and through more restrictive advertising rules. However, the FDA is primarily (if not solely) concerned with the former: alerting the public to medication risks without causing severely mentally ill patients to forego treatment out of fear of potential side effects.

In the case of pediatric antidepressants, the FDA decided the black-box warning was a necessary precaution. As a result, on October 15, 2004, the FDA issued a news release, "FDA Launches a Multi-Pronged Strategy to Strengthen Safeguards for Children Treated With

¹¹⁷ U.S. FOOD & DRUG ADMIN., FTS HHS FDA, TRANSCRIPT FOR FDA'S MEDIA BRIEFING ON THE SERIOUS MEDICAL HEALTH RISKS ASSOCIATED WITH THE DRUGS CHANTIX AND ZYBAN 1, 3-4 (JULY 1, 2009) (statements made in reference to the drugs Chantix and Zyban, in discussion of the increased risk of suicidality associated with these drugs.)

¹¹⁸ *Id.* at 13.

¹¹⁹ *Id.* at 6.

Antidepressant Medications,” detailing the labeling changes and the underlying rationale for the new, more severe warning.¹²⁰ The press release states,

“Today’s actions represent FDA’s conclusions about the increased risk of suicidal thoughts and the necessary actions for physicians prescribing these antidepressant drugs and for the children and adolescents taking them. Our conclusions are based on the latest and best science.”[quote from Dr. Lester M. Crawford, Acting FDA Commissioner]....In letters issued today, FDA directed the manufacturers of all antidepressant medications to add a “black box” warning that describes the increased risk of suicidality in children and adolescents given antidepressant medications and notes what uses the drugs have been approved or not approved for in these patients. FDA’s letters to the manufacturers also discuss other labeling changes designed to include additional information about pediatric studies of these drugs.¹²¹

To emphasize, the black-box warning applies to “36 drugs, including SSRI-class drugs, tricyclic antidepressants, and monoamine oxidase inhibitors.”¹²² The press release then goes on to describe the significance of the black-box warning and its implications for pediatric care,

A “black box” warning is the most serious warning placed in the labeling of a prescription medication.... Until now, only ten drug products approved for children contained a black box warning about their use in children. The new warning language does not prohibit the use of antidepressants in children and adolescents. Rather, it warns of the risk of suicidality and encourages prescribers to balance this risk with clinical need.¹²³

Also of note, the advisory,

included recommendations related to the frequency of psychotherapy and medication management visits. [And,] [t]he labeling change request explicitly stated, for the first time, that “ideally such observation would include at least weekly face-to-face contact with patients or their family members or caregivers during the first four weeks of treatment.”¹²⁴

On May 2, 2007, the FDA issued its most recent advisory: a news release entitled, “FDA Proposes New Warnings About Suicidal Thinking, Behavior in Young Adults Who Take

¹²⁰ U.S. FOOD & DRUG ADMIN., FDA LAUNCHES A MULTI-PRONGED STRATEGY TO STRENGTHEN SAFEGUARDS FOR CHILDREN TREATED WITH ANTIDEPRESSANT MEDICATIONS, NO. P04-97 (OCTOBER 15, 2004).

¹²¹ *Id.*

¹²² Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11,12 (2010).

¹²³ U.S. FOOD & DRUG ADMIN., FDA LAUNCHES A MULTI-PRONGED STRATEGY TO STRENGTHEN SAFEGUARDS FOR CHILDREN TREATED WITH ANTIDEPRESSANT MEDICATIONS, NO. P04-97 (OCTOBER 15, 2004).

¹²⁴ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11,12 (2010).

Antidepressant Medications.”¹²⁵ The 2007 advisory “proposed that makers of all antidepressant medications update the existing black box warning on their products’ labeling to include warnings about increased risks of suicidal thinking and behavior, known as suicidality, in young adults ages 18 to 24 during initial treatment (generally the first one to two months).”¹²⁶ The labeling changes came in response to a “comprehensive review of 295 individual antidepressant trial that included over 77,000 adult patients with major depressive disorder (MDD) and other psychiatric disorders, to examine the risk of suicidality in adults who are prescribed antidepressants.”¹²⁷ The review of these study findings began in 2005.¹²⁸ Then in late 2006, “FDA’s Psychopharmacologic Drugs Advisory Committee agreed that labeling changes were needed to inform health care professionals about the increased risk of suicidality in younger adults using antidepressants.”¹²⁹ While, according to the FDA, the findings revealed an increased risk of suicidality in young adults, the “scientific data did not show this increased risk in adults older than 24....”¹³⁰ Additionally, study findings support the conclusion that “adults ages 64 and older taking antidepressants have a decreased risk of suicidality.”¹³¹ Dr. Laurel Leslie, Associate Professor at Tufts University School of Medicine, and her co-authors suggest that there are “very real differences in the absorption, distribution, metabolism, excretion, efficacy, and safety of some medications in children and adolescents compared with adults.”¹³² This may explain why there is no indication of increased risk of suicidality in patients 25 years

¹²⁵ U.S. FOOD & DRUG ADMIN., FDA PROPOSES NEW WARNINGS ABOUT SUICIDAL THINKING, BEHAVIOR IN YOUNG ADULTS WHO TAKE ANTIDEPRESSANT MEDICATIONS, NO. P07-77 (MAY 2, 2007).

¹²⁶ *Id.*

¹²⁷ *Id.*

¹²⁸ *Id.*

¹²⁹ *Id.*

¹³⁰ *Id.*

¹³¹ *Id.*

¹³² Laurel K. Leslie et al., *The Food and Drug Administration’s Deliberations on Antidepressant Use in Pediatric Patients*, 116(1) PEDIATRICS 195, 196 (2005).

old or older, and a reduced risk of suicidality in patients 64 years old or older. Moreover, the 2007 press release stressed that “product labeling needed to reflect the apparent beneficial effect of antidepressants in older adults and to remind health care professionals that the disorders themselves are the most important cause of suicidality.”¹³³

Also in May 2007, “[b]ased on recommendations from the PDAC [the FDA Psychopharmacologic Drugs Advisory Committee], the FDA contacted GSK [GlaxoSmithKline]... and instructed GSK to delete Paxil-specific language in its labeling and to replace it with the class-wide label for SSRIs.”¹³⁴

The current black-box warning that appears on the labeling of all antidepressant medications is unchanged from the text proposed by the FDA in 2007.

V. AFTERMATH

The FDA black-box warning generated backlash from many practitioners and scholars who feared the warning would lead to a sharp decline in pediatric antidepressant prescription rates and thus worsen the problem of under-treatment of depression. Dr. Fassler explains that

[b]oth AACAP [American Academy of Child and Adolescent Psychiatry] and APA [American Psychiatric Association] did not... agree with the action ultimately taken by FDA in October 2004, to require a “black box warning” on all antidepressant medications prescribed for children and adolescents. We were concerned – and recent data substantiates our concern... that such a warning might inadvertently create a greater risk by discouraging families from seeking treatment and by dissuading physicians from the appropriate prescribing of these medications.¹³⁵

¹³³ U.S. FOOD & DRUG ADMIN., FDA PROPOSES NEW WARNINGS ABOUT SUICIDAL THINKING, BEHAVIOR IN YOUNG ADULTS WHO TAKE ANTIDEPRESSANT MEDICATIONS, NO. P07-77 (MAY 2, 2007).

¹³⁴ *Tucker v. SmithKline Beecham Corp.*, 701 F.Supp.2d 1040, 1046 (S.D. Ind. 2010).

¹³⁵ *FDA's Drug Approval Process: Up to the Challenge?: Hearing Before the Comm. on Health, Educ., Lab., and Pensions*, 109th Cong. 44 (2005) (statement of Dr. David Fassler, Board certified child and adolescent psychiatrist, member of the Board of Trustees for the American Psychiatric Association (APA), Clinical Associate Professor of Psychiatry at the University of Vermont).

He adds,

We are concerned that the available research findings do not support a warning that may be misinterpreted by some practitioners or parents to mean that antidepressant medications actually cause children and adolescents to commit suicide. Such a conclusion is simply not supported by the data.¹³⁶

A. TRENDS IN PEDIATRIC ANTIDEPRESSANT PRESCRIPTION RATES

While Dr. Fassler's concerns are well-founded, the decrease in pediatric antidepressant prescription rates and the corresponding increase in completed-suicide rates date back to the October 2003 warning, a full year before the black-box warning was issued. Anne Libby, Ph.D., Associate Professor of Pharmaceutical Outcomes Research in the Department of Clinical Pharmacy at the University of Colorado School of Pharmacy, et al. found that

Before the [October 2003] FDA advisory was issued, the diagnosis rate of pediatric depression was increasing, as was the rate of SSRI prescriptions for depression. After the FDA advisory, declines in treatment indicated a reversal of the previous trend: the overall rate of diagnosis declined, and among patients diagnosed, the proportion treated with antidepressants declined. Whereas there was substantial growth in diagnosis and antidepressant treatment of pediatric depression in primary care settings before the FDA advisory, there were substantial reversals afterward for both pediatricians and nonpediatrician primary care physicians. Treatment by psychiatrists increased after the FDA advisory, but not enough to compensate for the decline observed among primary care physicians.¹³⁷

More specifically, the authors concluded “that there was a 58% drop in the use of SSRIs among children diagnosed as having depression from the level to be expected if prescribing trends begun before this controversy had continued.”¹³⁸

Additionally, data provided by NDC Health, a company which “processes 5 billion health care transactions annually... and [has] connections with ‘more than 90 percent of U.S. pharmacies,’” revealed that in the month following the March 2004 FDA advisory, “the number

¹³⁶ *Id.*

¹³⁷ Anne M. Libby et al., *Decline in Treatment of Pediatric Depression After FDA Advisory on Risk of Suicidality With SSRIs*, 164(6) AM. J. PSYCHIATRY 884, 889 (2007).

¹³⁸ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11, 13 (2010).

of antidepressant prescriptions for those over the age of 18 declined by 10.7 percent, while prescriptions for those aged 18 and under declined 12.6 percent.”¹³⁹ Dr. Libby et al. cite similar findings. They write that in the three months following the March 2004 advisory, “all SSRI prescriptions for one pharmacy benefit manager declined by 20%.”¹⁴⁰ Two other early analyses based on “national pharmacy data... found 20-22% declines in antidepressant use among children and adolescents in 2004, before the issuance of the black box warning [in October 2004].”¹⁴¹ Such findings support the conclusion that despite wide criticism, “the black-box warning may not have been the primary factor contributing to the observed changes in treatment patterns.”¹⁴² Dr. Busch et al. write, “Confirming earlier studies, we found that the decline in antidepressant use began before the announcement of the black-box warning.”¹⁴³

Strangely, the data that most powerfully suggests that the black-box warning was the impetus for the decline in pediatric antidepressant prescription rates is the data endorsed by the FDA. The FDA’s analysis of pediatric antidepressant prescription trends can be described as follows:

Although the Medco Health Solutions, Inc, NDC Health, and Verispan analyses suggest that public health advisories regarding the safety of antidepressants have had direct effect on physician practice patterns, the FDA reported that it did not observe a decline in pediatric antidepressant prescribing during the September 2004 hearings. Rather, FDA officials asserted that the use of antidepressants by children and teenagers was still increasing. Using data provided by IMS Health Inc, the FDA found that pediatric antidepressant prescriptions continued to increase by 7% in 2004. Agency officials reported that the March 2004 advisory had no effect on prescription trends, with the

¹³⁹ Jim Rosack, *New Data Show Declines in Antidepressant Prescribing*, 40(17) PSYCHIATRIC NEWS 1, Sept. 2, 2005, <http://pn.psychiatryonline.org/content/40/17/1.1.full> (last visited January 20, 2011).

¹⁴⁰ Anne M. Libby et al., *Decline in Treatment of Pediatric Depression After FDA Advisory on Risk of Suicidality With SSRIs*, 164(6) AM. J. PSYCHIATRY 884, 885 (2007).

¹⁴¹ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11, 12 (2010).

¹⁴² *Id.* at 15.

¹⁴³ *Id.*

number of prescriptions for antidepressants given to children and teenagers growing almost 8% in the first half of 2004.¹⁴⁴

By arguing that pediatric antidepressant prescription levels did not decline prior to, or in response to, the March 2004 advisory, the FDA effectively concedes that if a decline in prescribing existed in the second half of 2004 or beyond, this effect would be more directly attributable to the black-box warning than to any prior FDA action on the subject.

Dr. Charles Nemeroff,¹⁴⁵ former Chairman of the Department of Psychiatry at Emory and former editor in chief of the influential journal of Neuropsychopharmacology, et al. provide an explanation for the apparent discrepancy between the two sets of data with regard to pediatric antidepressant prescription trends. They write, “Whereas the Verispan, Medco Health Solutions, Inc, and NDC Health data are patient-centric, with age information readily available for each prescription captured, the IMS Health Inc data are primarily based on a survey of drug use by pharmacies, with no collection of patient-specific information....”¹⁴⁶ Furthermore, the researchers expressed concern that “it remains unclear how the FDA distinguished between adult and pediatric prescriptions in its analysis.”¹⁴⁷

¹⁴⁴ Charles B. Nemeroff et al., *Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States*, 64 ARCHIVES GEN. PSYCHIATRY 466, 470 (2007).

¹⁴⁵ Following an investigation launched by two United States Senators based on allegations that Dr. Nemeroff had “earned more than \$2.8 million in consulting arrangements with drug makers from 2000 to 2007 [and] failed to report at least \$1.2 million of that income to his university and violated federal research rules,” Dr. Nemeroff voluntarily stepped down from his position at Emory University in October 2008. It is worth noting that GlaxoSmithKline is listed as one of the companies for which Dr. Nemeroff did extensive consulting and for which Dr. Nemeroff failed to disclose the true nature of his financial relationship.

<http://www.nytimes.com/2008/10/04/health/policy/04drug.html?pagewanted=1>. GlaxoSmithKline is the manufacturer of the antidepressant drug Paxil. However, because Dr. Nemeroff et al.’s article, *Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States*, is merely an interpretation of data collected by sources that have not been charged with impropriety and the analysis seems to consist of observations rather than advocacy, I have concluded that the findings of this article are likely reliable. Nonetheless, Dr. Nemeroff’s findings must be evaluated in the context of his significant non-disclosures and possible bias.

¹⁴⁶ Charles B. Nemeroff et al., *Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States*, 64 ARCHIVES GEN. PSYCHIATRY 466, 470 (2007).

¹⁴⁷ *Id.*

Despite the data relied upon by the FDA, the general consensus in the field remains that there was a significant decline in the total number of pediatric antidepressant medications between 2003 and 2005. Therefore, while scholars may disagree about which FDA action was most responsible for the sharp decline in prescription levels, it seems clear that changes in prescription levels occurred, at least in large part, because of FDA action. This assertion is supported by one of Dr. Gibbons et. al's studies, in which, "[they] found that the rates of SSRI prescriptions for children and adolescents decreased substantially in both the United States and the Netherlands after the U.S. and European regulatory agencies issued warnings of an increased risk of suicide in pediatric patients taking antidepressants."¹⁴⁸

The response to the Paxil-specific warning of June 2003 further supports the conclusion that pediatric antidepressant prescribing trends are affected by significant FDA action, even FDA action that does not reach the level of severity of a black-box warning. Dr. Busch et al. found

a substantial decline in the use of paroxetine and an increase in the use of fluoxetine during the periods consistent with the release of information by the FDA on the dangers of paroxetine (June 2003) and on the benefits of fluoxetine (October 2003). . . . Our results suggest that treatment initiation with paroxetine for children newly diagnosed as having major depressive disorder was relatively rare after the initial information about its risks was conveyed in the June 2003 FDA warning. We found that the total decline in overall antidepressant use was greater than the increase in fluoxetine use, indicating that providers were not simply switching from other antidepressants to fluoxetine. This finding suggests that at least in some cases, providers did not believe that the proven benefits of fluoxetine treatment outweighed the potential risks of pediatric SSRI use.¹⁴⁹

Additionally, although the black-box warning may not have been the particular FDA action to spark the trend of decreased prescribing, it certainly did not encourage a return to the previous, higher prescription levels, and may even have served as a catalyst for further declines. Based on a time line that extended past the date of the issuance of the black-box warning, Dr.

¹⁴⁸ Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164(9) AM. J. PSYCHIATRY 1356, 1358 (2007).

¹⁴⁹ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11, 15 (2010).

Gibbons et al. found that for children up to age 14 “overall SSRI use declined approximately 20% from 2003 to 2005, whereas new SSRI prescriptions declined 30% over the same period.”¹⁵⁰ Moreover, the NDC dataset, reviewed in September of 2005, “indicates that the decline in dispensing of antidepressant prescriptions...has continued for those aged 18 and under.”¹⁵¹ Unfortunately, more recent studies documenting the current antidepressant prescription rates are not available.

If the decline in prescription rates was attributable to a decrease in the number of depressed children, adolescents, and young adults, such a trend would not be alarming; in fact, such news would be very welcome. However, we would be doing a disservice to our youth if we reached the conclusion that significantly fewer individuals required treatment with antidepressant medication in 2005 than in 2003. As was previously discussed, depression is already both under-diagnosed and under-treated. It is therefore incredibly unlikely that a reduction in prescriptions reflects an improvement in the mental health of our youth rather than an exacerbation of the under-diagnosis and under-treatment phenomena that already plague our country. Thus, the trend towards fewer antidepressant prescriptions for children, adolescents, and young adults is disturbing to many. In an interview for an article in *Psychiatric News*, the publication of the American Psychiatric Association, Gail Griffith, a patient representative who sat on the FDA’s advisory panel, said, ““This picture is disastrous...The question I want answered is, Why?””¹⁵² Dr. Libby et al. provide a response to Ms. Griffith’s important question:

These changes may be driven by both providers and consumers. While providers are diagnosing depression less frequently, antidepressant prescriptions are also being filled less frequently. It is possible that part of the reduced rate of diagnosis of depression stems from new reluctance on the part of families, in the wake of the advisory, to seek

¹⁵⁰ *Id.* at 13.

¹⁵¹ Jim Rosack, *New Data Show Declines in Antidepressant Prescribing*, 40(17) *PSYCHIATRIC NEWS* 1, Sept. 2, 2005, <http://pn.psychiatryonline.org/content/40/17/1.1.full> (last visited January 20, 2011).

¹⁵² *Id.*

treatment or to disclose depressive symptoms. Similarly, providers may be writing prescriptions for antidepressants that families do not fill.¹⁵³

To Ms. Griffith, however, pinpointing the cause of the decline is critical because the root of the problem determines the remedial action that needs to be taken. She continues, “‘If the decline is coming from ‘physician reluctance,’... it may be due to lack of education or fear of liability or malpractice [associated with prescribing the drugs].... However,... if the reluctance is coming from the public, then we have an opportunity here to provide evidence and educate.’”¹⁵⁴

Also in question is whether the decline in youth SSRI prescription rates has been offset by an increase in another form of treatment for depression. Dr. Gibbons et al. believe that such a shift has not occurred. They explain,

Although some might expect that decreases in SSRI prescriptions would have led to increases in alternative antidepressant treatments, such as the newer non-serotonergic-specific antidepressants and tricyclic antidepressants, this does not appear to have been the case: similar decreases were seen in pediatric and young adult prescription rates for both these alternative antidepressant types (approximately 20% in the 5-14 years age range and approximately 10% in the 15-19 years age range). Furthermore, the majority of child and adolescent antidepressant prescriptions are for SSRIs. For example, in 2005, a total of 9,911,743 antidepressant prescriptions were written for the population under age 20, 65% of which were SSRIs, 20% for non-serotonergic-specific antidepressants, and 15% for tricyclic antidepressants....¹⁵⁵

Moreover, researchers have found “no evidence of increased use of other treatment options, such as psychotherapy, despite evidence of their effectiveness in treating suicide.”¹⁵⁶

These statistics and conclusions are, however, somewhat in tension with Dr. Nemeroff et al.’s finding of a slight increase in the prescribing of a non-SSRI medication. They state,

¹⁵³ Anne M. Libby et al., *Decline in Treatment of Pediatric Depression After FDA Advisory on Risk of Suicidality With SSRIs*, 164(6) AM. J. PSYCHIATRY 884, 889-90 (2007).

¹⁵⁴ Jim Rosack, *New Data Show Declines in Antidepressant Prescribing*, 40(17) PSYCHIATRIC NEWS 1, Sept. 2, 2005, <http://pn.psychiatryonline.org/content/40/17/1.1.full> (last visited January 20, 2011).

¹⁵⁵ Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators’ Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164(9) AM. J. PSYCHIATRY 1356, 1361 (2007).

¹⁵⁶ M. David Rudd et al., *What Every Psychologist Should Know About the Food and Drug Administration’s Black Box Warning Label for Antidepressants*, 40(4) PROF. PSYCHOL.: RES. & PRAC. 321, 323 (2009).

[O]ur analysis shows a slight shift in prescribing toward bupropion (a non-SSRI), which could stem in large part from physicians attributing the increased risk of suicidality primarily to SSRIs, even though bupropion is also labeled with a black box warning. Interestingly, we did not see any difference in trends within the SSRI class with respect to dosage or product selection, despite the fact that fluoxetine is the only SSRI formally approved by the FDA for the treatment of depression in children.¹⁵⁷

Perhaps what is most interesting about Dr. Nemeroff et al's finding is that despite the FDA's assurance that fluoxetine (Prozac) is safe and effective in children, adolescents, and young adults, the noted prescription trend was towards an unapproved, non-SSRI medication rather than the one approved SSRI medication.

While reasonable minds disagree about the prescription trends for non-serotonergic-specific antidepressants, both sets of researchers agree that any possible increase in non-serotonergic-specific antidepressant prescriptions was not of such magnitude so as to offset the decrease in SSRI prescriptions.

B. CORRELATIONS FOUND WITHIN PRESCRIPTION RATE TRENDS

In addition to charting the national pediatric antidepressant medication prescription rates and analyzing the trends found therein, scholars have also identified several trends and correlations at a micro-level.

As was briefly mentioned in one of the prior quotes from Dr. Libby et al., one effect of the risk disclosures was an increased reliance on psychiatrists in the treatment of depressed youth. Dr. Nemeroff et al. found this correlation as well. They write,

In addition to a decrease in prescribing of antidepressants to individuals younger than 18 years, the FDA actions have also resulted in a shift of care from generalists to psychiatrists. Although the number of depressed individuals younger than 18 years is small relative to the broader population, anecdotal evidence suggests over-demand for specialist services and, as a result, longer than historically observed waiting times for appointments.¹⁵⁸

¹⁵⁷ Charles B. Nemeroff et al., *Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States*, 64 ARCHIVES GEN. PSYCHIATRY 466, 471 (2007).

¹⁵⁸ *Id.* at 470-71.

Researchers also found several correlations between individual patient characteristics and prescription rates. Dr. Busch et al., for example, found that “[a]lthough rates of antidepressant use were higher among children of college-educated parents prior to the risk disclosures, these children were more likely to forgo antidepressant medication than children of less education parents after risk disclosures.”¹⁵⁹ Interestingly, differences in prescription volumes were also correlated with the type of payment used by the patient. Dr. Nemeroff et al. explain,

According to Medco Health Solutions, Inc, the number of patients younger than 18 years prescribed antidepressants decreased sharply by 18% in the first quarter of 2004 and by an additional 5% in the second quarter of 2004.... [The] analysis of the Verispan data... shows only a 5% decrease in the first quarter of 2004, with an additional 11% decrease in the second quarter of 2004. The difference in the magnitude of the effect on prescribing volume between the Medco Health Solutions, Inc. data (private payers only) and [the] analysis of the Verispan data (all payers) suggests that the prescribing behavior may have been slower to change for nonprivately insured individuals (eg, those with Medicaid insurance) than for the privately insured.¹⁶⁰

In another instance, the lack of correlation was what was surprising. Dr. Busch et al. write, “While we find treatment rates differ by patient risk aversion, we did not identify a differential decline in antidepressant use by patient risk aversion after risk disclosure.”¹⁶¹

C. INVERSE RELATIONSHIP BETWEEN ANTIDEPRESSANT PRESCRIPTION RATES AND SUICIDE RATES

Declining pediatric antidepressant prescription rates is concerning from the perspective of under-diagnosis and under-treatment of depression in children, adolescents, and young adults; we, as a society, have an interest in diagnosing and treating those among us who are suffering. However, the decline in prescription rates is even more concerning once we consider the well-

¹⁵⁹ Susan H. Busch et al., *Characterizing Declines in Pediatric Antidepressant Use After New Risk Disclosures*, 68(1) MED. CARE RES. REV. 96, ABSTRACT (2011).

¹⁶⁰ Charles B. Nemeroff et al., *Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States*, 64 ARCHIVES GEN. PSYCHIATRY 466, 470 (2007).

¹⁶¹ Susan H. Busch et al., *Characterizing Declines in Pediatric Antidepressant Use After New Risk Disclosures*, Unpublished Version 1, 13 (2010) (available at faculty.fuqua.duke.edu/~dbr1/health/Busch.pdf, last visited January 20, 2011).

documented inverse relationship between antidepressant use and completed suicides. Lower antidepressant prescription rates means less treatment for the vulnerable individuals afflicted with devastating mental illness. This in turn means that those needy, untreated individuals are at increased risk of taking drastic action: committing suicide. Dr. Gibbons et al., along with many of their colleagues, explain that “countries with higher rates of SSRI prescriptions ha[ve] lower rates of suicide in children and young adolescents.”¹⁶² This inverse relationship between antidepressant prescription rates and completed suicides has been established by many scholars and has been substantiated by both domestic and international data sets. Dr. Busch and her co-author, Colleen Barry, Ph.D., Associate Professor of Health Policy and Management at the John Hopkins Bloomberg School of Public Health, reference a Finish study in support of the assertion that this phenomenon holds true across countries. They write, “[a] study from Finland... found that current use of an antidepressant...is associated with both an increased risk of *attempted* suicide, and a decreased risk of *completed* suicide and mortality” (emphasis original).¹⁶³ Similarly, Dr. Gibbons et al. discusses statistics from the Netherlands that support the same conclusion. They offer, “In the Netherlands, there was a 22% decline in child and adolescent SSRI prescription rates and a 49% increase in suicides in this age group [individuals up to age 19] from 2003 to 2005.”¹⁶⁴

More specifically, Dr. Gibbons et al. provide an account of the changes in the U.S. suicide rates following the FDA advisories. They write,

The data available from the CDC on U.S. suicide rates at the time of the study (through 2004) revealed that there was already a 14% increase in child and adolescent suicide rates

¹⁶² Robert D. Gibbons et al., *The Relationship Between Antidepressant Prescription Rates and Rate of Early Adolescent Suicide*, 163(11) AM. J. PSYCHIATRY 1898, 1901 (2006).

¹⁶³ Susan H. Busch & Colleen L. Barry, *Pediatric Depression Treatment in the Aftermath of the Black Box Warning: Implications for Prescription Drug Policy*, 28(3) HEALTH AFF. (MILLWOOD) 724, 728 (2009).

¹⁶⁴ Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators’ Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164(9) AM. J. PSYCHIATRY 1356, 1359 (2007).

from 2003 to 2004. Since 1988, the U.S. child and adolescent suicide rate has consistently decreased with two exceptions – a 1% increase in 1994 and a 3% increase in 2000. The 14% increase from 2003 to 2004 is the first increase of this magnitude in the child and adolescent suicide rate since the CDC began systematically collecting suicide data in 1979. While only a small decrease in the SSRI prescription rate for U.S. children and adolescents occurred from 2003 to 2004, the public health warnings may have left some of the most vulnerable youths untreated.¹⁶⁵

As Dr. Gibbons et al. make abundantly clear, a 14% increase in the suicide rate is enormous.

Also worth emphasizing is the reactivity in the suicide rates to slight changes in antidepressant prescription rates. While other researchers have concluded that the decrease in pediatric antidepressant prescription rates was significantly larger than that which Dr. Gibbons et al. describe, Dr. Gibbons et al.'s findings suggest that even a slight decrease in the prescription rate can produce a spike in suicide rates. These findings have led Dr. Gibbons et al. to be quite critical of the FDA advisories:

If the FDA's conclusion that there may be a causal link between suicide and antidepressants (which was the basis for the black box warning) were correct, we would have expected to see decreases in the suicide rate during the period of declining SSRI prescription rates, but instead we saw an increase in suicide rates, and the increase was the greatest in the age range most affected by the decline in SSRI prescription rates. This finding, which is consistent with results from our previous ecological studies of the U.S. data suggests that SSRIs confer a protective effect¹⁶⁶....If the intent of the pediatric black box warning was to save lives, the warning failed, and in fact, it may have had the opposite effect; more children and adolescents have committed suicide since it was introduced.¹⁶⁷

D. OTHER CONCERNS SURROUNDING THE DECLINE IN ANTIDEPRESSANT PRESCRIPTION LEVELS

Dr. Thomas Insel, Director of the National Institute for Mental Health (NIMH), expresses another concern associated with the decline in pediatric antidepressant prescriptions. He states,

“Our sense from this and similar data is that at the same time that there's been a drop in use of antidepressants, there has been a compensatory increase in the use of atypical antipsychotics in this population... And that is of great concern because we have very

¹⁶⁵ *Id.*

¹⁶⁶ *Id.* at 1360.

¹⁶⁷ *Id.* at 1361-62.

little safety data and very little evidence of efficacy, for that matter. These drugs simply haven't been studied much in children.”¹⁶⁸

Yet another concern with the decline in antidepressant prescription levels is an unintended effect on the treatment patterns for adult depression. Dr. Gibbons et al. found that “[i]n the United States, the reduction in SSRI prescriptions spilled over to affect prescriptions for adults up to age 60 as well.”¹⁶⁹ This is particularly problematic because according to the text of the black-box warning, “[s]hort-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24....”¹⁷⁰ Dr. Mark Olfson, Professor of Clinical Psychiatry at Columbia University, adds, that “[t]here is also stronger empirical support for the efficacy of antidepressants in the treatment of adult than child mood and anxiety disorders.”¹⁷¹ Like Dr. Gibbons et. al, Dr. Olfson and his co-authors found that “significant decelerations in the rate of growth of all antidepressant use were also evident for adults.”¹⁷² Dr. Olfson and his fellow researchers offered the possible explanation that “[t]hese trends may reflect spreading concern over the safety of antidepressants in general.”¹⁷³ The FDA advisories were aimed at alerting the public about a possible risk associated with *pediatric* use of antidepressant medications; however, the FDA did not intend create a general skepticism of antidepressant medications among individuals of all ages.

¹⁶⁸ Jim Rosack, *New Data Show Declines in Antidepressant Prescribing*, 40(17) PSYCHIATRIC NEWS 1, Sept. 2, 2005, <http://pn.psychiatryonline.org/content/40/17/1.1.full> (last visited January 20, 2011).

¹⁶⁹ Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164(9) AM. J. PSYCHIATRY 1356, 1358 (2007).

¹⁷⁰ U.S. FOOD & DRUG ADMIN., REVISIONS TO PRODUCT LABELING, <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM173233.pdf> (last visited January 20, 2011).

¹⁷¹ Mark Olfson et al., *Effects of Food and Drug Administration Warnings on Antidepressant Use in a National Sample*, 65(1) ARCHIVES GEN. PSYCHIATRY 94, 99 (2008).

¹⁷² *Id.*

¹⁷³ *Id.*

E. ADDITIONAL FINDINGS

The FDA advisories were twofold: they aimed to warn of the potential risks associated with pediatric antidepressant use and to emphasize the need for increased physician monitoring of patients being treated with an antidepressant medication regimen. As early as the October 2003 letter addressed to health care professionals, the FDA recommended increased doctor-patient contact for both children and adults beginning a course of medication treatment.¹⁷⁴ Specifically, the FDA advised that “[c]lose supervision of high-risk patients should accompany initial drug therapy.”¹⁷⁵ Therefore, in addition to evaluating the effects of the FDA’s cautionary statements, researchers have also studied the response to the FDA’s recommendation of additional patient supervision, especially in the first few weeks of treatment.

Elaine Morrato, Dr.Ph., Assistant Professor of Health Systems, Management, & Policy at the Colorado School of Public Health, et al. tracked the physician response to the FDA supervision recommendation. They write,

Overall, we did not find an increase in frequency to face-to-face visits after the FDA advisory was issued in October 2003. The proportion of pediatric patients meeting FDA frequency-of-visit recommendations was less than 5% before the advisory was issued, and it did not change significantly afterward. The low frequency of follow-up we observed was similar to preadvisory rates seen in a large managed-care organization.¹⁷⁶

Dr. Busch et al. similarly “found that the FDA warnings encouraging increased use of monitoring when prescribing antidepressants had no effect.”¹⁷⁷

It is quite unfortunate that the FDA’s recommendations with respect to increased patient supervision were not incorporated into practice. It is possible that close physician supervision

¹⁷⁴ U.S. FOOD & DRUG ADMIN., REPORTS OF SUICIDALITY IN PEDIATRIC PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS FOR MAJOR DEPRESSIVE DISORDER (MDD) (OCTOBER 27, 2003).

¹⁷⁵ *Id.*

¹⁷⁶ Elaine H. Morrato et al., *Frequency of Provider Contact After FDA Advisory on Risk of Pediatric Suicidality With SSRIs*, 165(1) AM. J. PSYCHIATRY 42, 48 (2008).

¹⁷⁷ Susan H. Busch et al., *Antidepressants and Suicide Risk: How Did Specific Information in FDA Safety Warnings Affect Treatment Patterns?*, 61(1) PSYCHIATRIC SERVICES 11, 15 (2010).

would have provided wary patients and their parents with a sense of security that would have allowed them to initiate a course of medication treatment despite the risks. If attention from health care providers could have lessened the fear associated with the pediatric use of antidepressant medication thereby reducing the decline in prescribing rates, the significant increase in the national suicide rates may have been avoided.

VI. RECOMMENDATIONS

We have now come full circle, back to question posed in the first paragraph of this paper: given this incredibly difficult situation, what was the FDA to do?

In a country like ours, where access to information is seen as a fundamental right, non-disclosure of the finding of increased risk of suicidality would have been a death sentence for the FDA. This is evidenced by a statement made by Joseph Barton, then-Chairman of the Subcommittee on Oversight and Investigations of the Energy and Commerce Committee of the House of Representatives, in the congressional hearing entitled, “FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-depressant Use by Children.” At that hearing, then-Chairman Barton offered some harsh words about what he perceived to be the FDA’s slow response to the data revealing an increased risk of suicidality:

One final issue that I want an answer today from the FDA: When [did] the FDA first become aware of the potential link between anti-depressants and suicidality in children, and what did they do to get to the bottom of it? Throughout our investigation, we have learned that as far back as 1996,... a medical reviewer at FDA, Dr. James Knudsen, raised the question of an increase in suicidality in pediatric clinical trials of the drug called Zoloft.... The fact that children taking anti-depressants were experiencing psychiatric adverse events at greater rates than adults was known at the agency as far back as 1996 and 1997. The committee wants to know what did the agency do to respond to these concerns? ... The mission of the FDA is not to protect the FDA’s internal workings, but to promote and protect the public health by helping safe and effective products reach the market by monitoring for safety, by disclosing the accurate, science based information, and for providing this in a clear and timely fashion to the American people. Is the FDA accomplishing its mission with anti-depressants used by children? I would have to say the record is open on that, and I would say that, unless we get

some very straight answers at today's hearing, it is probably going to be answered that the FDA is not fulfilling its mission in this particular issue.¹⁷⁸

Congressman Greg Walden of the State of Oregon echoed these sentiments:

Giving parents and doctors as much information about the benefits or lack thereof and the risks associated with drugs that are being prescribed for millions, tens of millions, of our Nation's children should be at the forefront of the FDA's mission.... I hope to get some answers from the agency about the timeline of events in terms of what they told the public about safety concerns raised within the agency about children taking these drugs, and then when they told the public. As we know, the British drug regulatory agency seemed to act much swifter on this than the FDA with the same data. So I think it is a fair question to ask this agency: Was the public health served by the longer deliberative process in this case?¹⁷⁹

Then-Congressman Mike Ferguson of the State of New Jersey further emphasized the need for disclosure. In his remarks at the congressional hearing, he stressed "how vital it is that doctors receive all the latest relevant study data and results so they can make the most informed decisions possible on the safety of the drugs they are prescribing."¹⁸⁰ These statements make exceedingly clear that it would be utterly unacceptable to Congress, to which the FDA is accountable, and to the masses, for the FDA to withhold access to information of public importance.

While one could argue that the FDA could have buried this information and none of us, including Congress, would have been the wiser, I find this view unrealistic. The likelihood of "secret" information being leaked to the public is great. And, once it is revealed that the information was buried purposefully, thereby depriving the American people of their ability to make fully-informed decisions, scandal would ensue. Intentional non-disclosure of significant health information, especially information relating to an increased risk of suicidality, would lead

¹⁷⁸ *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 3-4 (2004) (statement of Rep. Barton, Chairman, House Comm. on Energy and Com.).

¹⁷⁹ *Id.* at 8-10 (statement of Rep. Walden, Member, House Comm. on Energy and Com.).

¹⁸⁰ *Id.* at 16 (statement of Rep. Ferguson, Member, House Comm. on Energy and Com.).

to a severe drop in consumer confidence in the FDA and harsh backlash from Congress.

Speaking from a political standpoint, there was no way in which the FDA could have withheld information on an increased risk of suicidality without jeopardizing public confidence in the Agency as well as its funding from Congress. With that said, however, I think there were gentler and less scary ways in which to present the findings on suicidality that would not have produced such a strong, negative reaction from the public.

First, I would have advised against using the term “suicidality.” While “suicidality” may be a succinct term of art, for those who are not familiar with the scientific meaning, “increased risk of suicidality” sounds confusingly similar to “increased risk of committing suicide.” A quote from Dr. Fassler, found earlier in this paper, expresses this concern as well. In discussing the black-box warning, Dr. Fassler stated, “We are concerned that the available research findings do not support a warning that may be misinterpreted by some practitioners or parents to mean that antidepressant medications actually cause children and adolescents to commit suicide. Such a conclusion is simply not supported by the data.”¹⁸¹ Although such a suggestion would have added length to the FDA advisories and black-box warning, I would have recommended that the FDA avoid the word “suicidality” entirely, and instead rely solely on the phrase “suicidal ideation and nonfatal suicide attempts.” There are no variations of the word “suicide” that do not instill fear; however, the more precise the FDA is in its descriptions, the less the public is left to speculate and reach an even more frightening conclusion as to what the FDA means to convey through its warnings.

¹⁸¹ *FDA’s Drug Approval Process: Up to the Challenge?: Hearing Before the Comm. on Health, Educ., Lab., and Pensions*, 109th Cong. 44 (2005) (statement of Dr. David Fassler, Board certified child and adolescent psychiatrist, member of the Board of Trustees for the American Psychiatric Association (APA), Clinical Associate Professor of Psychiatry at the University of Vermont).

Second, I believe the advisories could have been better framed so as to emphasize the benefits of antidepressant medications and encourage their continued use. The October 2003 letter to health care professionals, for example, included statements like “[w]hile occurrences of suicidality are not unexpected in patients with MDD, preliminary data suggest an excess of such reports for patients assigned to several of these antidepressant drugs compared to those assigned to placebo,” “[y]ou may also be aware of press and medical journal reports of suicide attempts and completed suicides in pediatric patients receiving antidepressants,” and **“FDA emphasizes that these drugs must be used with caution.”**¹⁸² Although the advisory does mention that there were no completed suicides in the placebo-controlled trials upon which the FDA’s conclusion was based, this is the only reference to any “redeeming” features of pediatric antidepressants. This one statement, embedded in a letter warning of the serious risks of pediatric antidepressant medications could easily be overlooked by a doctor skimming this letter in the course of a very busy day. Moreover, even if read, the sole “reassuring” remark is overshadowed by the powerful cautionary statements that surround it. Doctors are acutely concerned with legal liability for their medical choices. If faced with a letter from the FDA that states “there have been no reports of completed suicides[;] [h]owever, FDA has not at this point been able to rule out an increased risk of suicidality for any of these drugs...” and concludes with a boldfaced warning that **“FDA emphasizes that these drugs must be used with caution,”** it is entirely possible, if not probable, that doctors would interpret this advisory to mean, “prescribe pediatric antidepressant drugs at your own risk.”¹⁸³ It is quite foreseeable that such a letter would serve as a deterrent to the prescribing of pediatric antidepressant medications.

¹⁸² U.S. FOOD & DRUG ADMIN., REPORTS OF SUICIDALITY IN PEDIATRIC PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS FOR MAJOR DEPRESSIVE DISORDER (MDD) (OCTOBER 27, 2003).

¹⁸³ *Id.*

A more balanced advisory that discussed the “ecologic data suggesting that increasing prescriptions for antidepressant drugs in adolescents are associated with a decrease in adolescent suicide,”¹⁸⁴ and acknowledged that “up to 40-60% [of patients treated with pediatric antidepressants] will demonstrate an improvement in suicidal ideation and similar proportions will demonstrate a meaningful reduction in other symptoms of depression,”¹⁸⁵ would have more fairly presented the truth about pediatric antidepressant use. Furthermore, the FDA should have mentioned, if not emphasized, that, as Dr. Gibbons writes, “studies clearly show that the greatest risk of suicide is depression.”¹⁸⁶ Additionally, I would have liked to see the FDA include a statement such as, “The data presented in this health advisory is only preliminary and further investigation must be done before the FDA is able to issue any firm recommendations or come to any certain conclusions. In the mean time, the FDA wishes to emphasize that antidepressant medications remain an important tool in the treatment of pediatric and adolescent depression. The FDA trusts that health professionals will consider the risks detailed in this advisory in the context of their many years of experience with the use of antidepressant medications in youth and their knowledge of the benefits these medications confer.” Since the results of the meta-analysis were not available at the time of the October 2003 advisory, and the advisory was based solely on preliminary findings from a limited number of studies, the FDA should have expressed its concerns with regard to pediatric antidepressant use more tentatively. Especially because the FDA did not have strong evidence on which to base its conclusion, the FDA should have balanced its cautionary statements with acknowledgments of the usefulness and importance of pediatric antidepressant medications.

¹⁸⁴ Tarek A. Hammad et al., *Suicidality in Pediatric Patients Treated With Antidepressant Drugs*, 63 ARCHIVES GEN. PSYCHIATRY 332, 338 (2006).

¹⁸⁵ U.S. FOOD & DRUG ADMIN., ACNP COMMENTS ON SSRI USE IN ADOLESCENTS 1, 5 (2004).

¹⁸⁶ Nicholas Bakalar, *Suicide Findings Question Link to Antidepressants*, N.Y. TIMES, July 10, 2007, <http://www.nytimes.com/2007/07/10/health/psychology/10depre.html> (last visited January 20, 2011).

Drs. Bush and Barry express a similar concern with respect to how the information was framed. They state, “In the case of pediatric antidepressant use, parents may overemphasize the comparatively small safety risks associated with their child taking antidepressants compared with the risks of untreated depression.... Framing the possible consequences of pediatric antidepressant use in terms of suicidality risk (a loss frame), may have led more individuals to forego antidepressant treatment.”¹⁸⁷

I have singled out the October 2003 advisory because first impressions are often long-lasting. Even if later advisories were framed in ways that were less hostile to pediatric antidepressant use, the harm was done long before those advisories reached the masses. As the Supreme Court of Oregon once wrote, “It is not an easy task to unring a bell, nor to remove from the mind an impression once firmly imprinted there....”¹⁸⁸ Unfortunately, judging from the antidepressant prescription rate trends detailed in the previous section, the cautionary statements made in the October 2003 FDA advisory rang too loudly and were accepted too eagerly.

The text of the FDA advisories, even if addressed only to health care providers, reaches the public through media reporting. According to a manuscript by Drs. Busch and Barry, “[o]ver half of the American public describes national, local, or cable news as their most important source of health information, and providers also report learning about new health issues via the news media.”¹⁸⁹ This statistic is frightening in that it gives the media tremendous ability to mold the health messages received by the public. When the media, rather than the FDA, presents the information to the public, there are always risks of misrepresentation of scientific data and of unbalanced portrayals. In 2010, Drs. Barry and Busch published the results of a study they had

¹⁸⁷ Susan H. Busch & Colleen L. Barry, *Pediatric Depression Treatment in the Aftermath of the Black Box Warning: Implications for Prescription Drug Policy*, 28(3) HEALTH AFF. (MILLWOOD) 724, 727 (2009).

¹⁸⁸ *State v. Rader*, 62 Or. 37, 40 (1912).

¹⁸⁹ Susan H. Busch & Colleen L. Barry, *Pediatric Depression Treatment in the Aftermath of the Black Box Warning: Implications for Prescription Drug Policy*, 28(3) HEALTH AFF. (MILLWOOD) 724, 727 (2009).

conducted “to assess the quality and content of and overall impression conveyed in the news reporting on FDA warnings pertaining to pediatric antidepressant use, among national and regional news sources with large circulation or viewership.”¹⁹⁰ Their study produced a number of interesting findings, namely:

The overwhelming majority of news reports accurately described the association between pediatric antidepressant use and suicidality rather than suicide itself, an indicator of good-quality reporting. However, other key health messages highlighted in FDA warnings, pertaining to the importance of monitoring, the need to taper doses during medication discontinuation, and FDA approval of fluoxetine to treat depression in children, often were absent from news reports. These findings suggest that including key health messages in FDA safety warnings was not sufficient to ensure communication to the public through the lay press, although this information might have mitigated the risk of pediatric antidepressant use.... Simply including key health messages in FDA press releases was not sufficient to ensure that journalists mentioned this information in news stories. News stories, in particular television news, were more likely to include anecdotes of children harmed by antidepressants than children helped, whereas expert source quotations more likely to emphasize the benefits of antidepressants over their risks.... Given evidence that patients may weight anecdotal versus statistic evidence disproportionately, the news coverage use of anecdotes of children harmed might have led to larger decreases in pediatric antidepressant use than would have occurred otherwise.¹⁹¹

This study supports the previous point that the way in which information is framed in the FDA advisories matters. This is true because media reports, if accurate, are grounded in the text of the FDA statements. More balanced press releases, then, should lead to more balanced reporting.

Another important take-away from the study by Drs. Barry and Busch is that news reporting, while incredibly influential on public opinion, cannot be relied upon to provide the public with a comprehensive understanding of the FDA recommendations. The news media is, in the words of Drs. Busch and Barry, “an imperfect conduit for communicating health

¹⁹⁰ Colleen L. Barry & Susan H. Busch, *News Coverage of FDA Warnings on Pediatric Antidepressant Use and Suicidality*, 125 PEDIATRICS 88, 93 (2010).

¹⁹¹ *Id.*

information to the public.”¹⁹² If the FDA notices that, for example, media reports have focused on anecdotal evidence to the exclusion of scientific findings, or have omitted key points such as the need for increased monitoring of patients beginning an antidepressant medication regimen, the FDA should respond to these deficiencies in reporting by issuing another public statement clarifying its position. If health information is warped before it reaches the general public, the FDA certainly has the right, if not also the responsibility, to correct any misperceptions and fill in any blanks. The need for FDA monitoring of news coverage of its public releases is evidenced by a statement from Drs. Busch and Barry. They write, “Patients learn about drugs through interactions with providers, direct-to-consumer advertising and the news media. While patients have greater access to medical information than in the past, they are still limited in their ability to decipher often complex health information.”¹⁹³ Moreover, action taken by the FDA in response to media reporting need not create hostilities between the FDA and the news media; public relations specialists are most certainly able to craft clarifying messages from the FDA that would not be offensive to journalists or news stations. Although many FDA press releases may be of little concern to the average American, advisories regarding the increased risk of suicidality associated with pediatric antidepressants do not fall into that category. Information on the issue of antidepressant-related suicidality carries great weight because it affects the future behavior of millions of depressed children, adolescents, and young adults, as well as their parents. When a topic is of such great significance, it is crucial that the public receives both correct and complete information before committing to, or foregoing, a particular type of treatment. Here, better utilization of the media by the FDA would have been served the public interest.

¹⁹² Susan H. Busch & Colleen L. Barry, *Pediatric Depression Treatment in the Aftermath of the Black Box Warning: Implications for Prescription Drug Policy*, 28(3) HEALTH AFF. (MILLWOOD) 724, 727 (2009).

¹⁹³ *Id.* at 726.

In addition to better controlling the message presented to the general public, the FDA, believing that fluoxetine (Prozac) is the safest and most efficacious pediatric antidepressant medication, as is implied by the FDA's sole approval of fluoxetine for use in youths, could have done more to encourage fluoxetine prescriptions. Drs. Bush and Barry note that

[a]ntidepressants were the most heavily promoted drug class in 2005, with over 1 billion dollars in promotional spending. While antidepressants were not specifically promoted for use in children, the high level of spending on detailing and direct-to-consumer advertising and the availability of free samples may have included prescribing patterns for children. Fluoxetine was [already] available in generic form, so there was little incentive for Eli Lilly to promote its use.¹⁹⁴

If the FDA wished to see a preference among prescribers for fluoxetine, it should have offered a financial incentive to Eli Lilly to promote the drug despite its release in generic form.

Alternatively, the FDA could have included a statement in one or more of its health advisories recommending that when treating children, adolescents, and young adults, health care professionals first consider fluoxetine before prescribing another antidepressant medication.

There were also a number of options available to the FDA that it did not take, and I think rightfully so. In order to ensure the implementation of its recommendation of increased monitoring of patients beginning an antidepressant medication regimen, the FDA could have promulgated a mandatory supervision schedule. Under the Food and Drug Administration Amendments Act (FDAAA), which took effect in March 2008, the FDA has the authority to impose a mandatory Risk Evaluation and Mitigation Strategy (REMS).¹⁹⁵ While it is unclear whether the FDA had the authority to issue a mandatory supervision schedule before March 2008, the FDA certainly has the power to do so now, and has chosen, despite this power, not to impose a REMS on pediatric antidepressant drugs.

¹⁹⁴ *Id.* at 727.

¹⁹⁵ U.S. FOOD & DRUG ADMIN., QUESTIONS AND ANSWERS ON THE FEDERAL REGISTER NOTICE ON DRUGS AND BIOLOGICAL PRODUCTS DEEMED TO HAVE RISK EVALUATION AND MITIGATION STRATEGIES (MARCH 26, 2008).

A REMS is imposed in order to “manage a known potential serious risk associated with a drug or biological product.”¹⁹⁶ A REMS, which can include “a Medication Guide, Patient Package Insert, a communication plan, elements to assure safe use, and an implementation system,” can be required by the FDA if it “finds that [a REMS] is necessary to ensure that the benefits of the drug or biological product outweigh the risks of the product.”¹⁹⁷ Additionally, drugs and biological products that have already received FDA approval may also be deemed to have REMS.¹⁹⁸

Therefore, under its REMS authority, the FDA could have announced that any doctor who does not have contact within the first week of treatment with a patient initializing antidepressant medication would be deemed negligent. If the FDA declared that the appropriate standard of care is at least one doctor’s visit within the first week of medication treatment, physicians who failed to comply with this recommendation would effectively be inviting malpractice litigation. Again, malpractice liability is a major concern for those in the healthcare industry; by altering the standard of care, the FDA would in turn alter physician behavior.

Such a plan though, would likely be ineffective unless doctors were unable to prescribe, at the initialization stage, more than one week of antidepressant medications to children, adolescents, and young adults. While a reshaping of the negligence rules would incentivize doctors to contact their patients and request more frequent office visits, patients (or their parents), if given multi-month prescriptions, could deem the extra office visits unnecessary and refuse the additional supervision. In refusing to comply with the doctor’s request that the patient come in for more frequent monitoring, the patient would waive his/her ability to sue for medical malpractice based on a breach of the FDA’s standard of care for patient supervision. So long as

¹⁹⁶ *Id.*

¹⁹⁷ *Id.*

¹⁹⁸ *Id.*

the patient (or his parent) refused the monitoring, the doctor would be released from any malpractice liability related to the FDA's mandatory supervision schedule. As such, a stand-alone, mandatory supervision schedule would probably not be a powerful enough incentive for change.

I believe the FDA was correct in avoiding these measures because the coupling of increased physician liability for antidepressant prescribing with the shorter prescription lengths would likely lead to an undesired result: a significant decline in pediatric antidepressant prescribing, to the detriment of our youth. Unfortunately, the most probable effect of burdening the pediatric antidepressant prescribing process would be many fewer prescriptions. From the physician point of view, with this new system in place, any pediatric antidepressant prescription exposes him/her to potential malpractice liability. From the parent point of view, such extreme action taken by the FDA signals that antidepressant medications are dangerous. Limiting prescription lengths in order to force closer physician supervision has an expressive function; it suggests that this particular medication is so risky that it requires a mandatory monitoring mechanism, and as result, the medication and the risk are both not worth taking.

Additionally, speaking pragmatically, a requirement that one's child visit the doctor every week during the initialization of treatment is burdensome to the parent. The parent might need to take time off from work in order to be available to bring to the child to the doctor. Also, visits to the doctor are often accompanied by co-payments, if the patient is covered by an insurance policy, or large out-of-pocket payments, if the patient is uninsured. Many families in this country cannot afford time off from work or frequent payments for healthcare. Similarly, many families would find it difficult to visit a pharmacy every week and pay the corresponding medication costs.

Furthermore, from the perspective of the healthcare system, strict supervision guidelines would require scheduling thousands of additional appointments with healthcare providers. This would burden the healthcare system and possibly result in extensive waiting periods. As has been mentioned several times already in this paper, depression in youth remains under-diagnosed and under-treated. Long wait times would discourage parents from taking their children to the doctor to be evaluated for symptoms of depression. The more difficult it is for children to be screened and then treated for depression, the greater the number of children who will remain undiagnosed and untreated.

As was previously discussed at length, any decline in antidepressant prescription can have a disastrous effect on suicide rates. Therefore, any FDA action which will result in a decrease in prescribing of pediatric antidepressant medications would be counter-productive, and thus, should be avoided.

Moreover, such a significant intrusion into the practice of medicine by the FDA would be extremely unpopular from a political standpoint. It goes without saying that the medical community would greatly resent the FDA's usurpation of its power to determine appropriate standards of care and proper prescribing procedures. Doctors are professionals who are valued for their judgment and knowledge; if the FDA were to dictate the practice of medicine, the FDA would undermine society's perceptions of doctors as professionals. Additionally, doctors consider the totality of the patient's circumstances before deciding on the right course of treatment for that individual. Rules that apply across the board, to all patients, remove doctor discretion to treat each patient individually based on his particularized needs.

For the same reason, I believe the FDA acted properly when it chose not to contraindicate or ban the use of antidepressant medications in children, adolescents, and young adults.

Some, including then-Representative Bart Stupak, expressed the belief that “these anti-depressants should be banned until the jury comes back with proof that they are safe and that they work....Increased risk, no matter how large or small, is still an increased risk for suicidal behavior.”¹⁹⁹ While then-Representative Stupak’s intentions are good, this paper suggests that the problem with the FDA’s action with respect to pediatric antidepressant warnings was that the cautionary statements were too effective, not that more drastic measures were needed to protect the public from harm. The FDA warnings served as a deterrent to antidepressant prescribing, which in turn led to an uptick in the rate of completed suicides. Banning the prescription of pediatric antidepressants would only have exacerbated this tragic result.

Moreover, then-Representative Stupak’s statements rely on a faulty premise: that antidepressant drugs are not effective in children. As has been oft-mentioned in this paper, the FDA has approved fluoxetine for use in the pediatric population, thereby certifying both its safety and efficacy. Furthermore, the majority of researchers and health care providers, and the FDA itself, would likely defend the use of other, non-FDA-approved antidepressants in children, adolescents, and young adults. In support of this, I will rely again on the quote from Dr.

Temple:

To date, clinical trials evaluating six other current generation anti-depressants approved for adults have not met FDA’s standards for establishing efficacy in the child/adolescent population. Nevertheless, there is widespread belief among treating physicians that these products do in fact work and that the “negative” results are in fact inconclusive. Negative trials are not necessarily informative in MDD trials because they may be an indication of inadequate trials rather than evidence of benefit.²⁰⁰

¹⁹⁹ *FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children: Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Com.*, 108th Cong. 18 (2004) (statement of Rep. Stupak, Member, House Comm. on Energy and Com.).

²⁰⁰ *Id.* at. 70 (statement of Dr. Robert Temple, Director of the Office of Medical Policy, Center for Drug Evaluation and Research at the FDA).

Then-Representative Stupak suggested, in the alternative, that “[t]he FDA should...require parents to sign an informed consent before treatment can begin.”²⁰¹ This is yet another possible way in which the FDA could have responded to its conclusion that pediatric antidepressant use is associated with an increased risk of suicidality, but chose not to. The idea of requiring informed consent is problematic in that there is significant disagreement among researchers about the risks associated with pediatric antidepressant use. As the section on suicidality reflects, some researchers remain unconvinced that there is any increased risk of suicidality associated with the use of pediatric antidepressant medications. Such disagreement would make a detailed explanation of the risks difficult. Informed consent is dependent on the signing party being aware of and accepting the risks associated with the treatment. Some experts would contend that there are no risks specific to pediatric antidepressant medications of which the parent must be informed. Additionally, an informed consent requirement would have a similar expressive function as the one-week-only prescriptions in that it would signal an especially dangerous product. Incorporating an informed consent requirement then would likely have led to a sharp decline in pediatric antidepressant prescription rates, the exact outcome that we wish could have been prevented.

Lastly, my final recommendation does not have to do with the FDA’s actions, but rather, earlier identification of depressed individuals in order to improve treatment outcomes. Dr. Bridge et al. stress the importance of heeding the early warning signs in order to treat the symptoms before they reach a level of diagnosable major depression. They write, “Given that anxiety is a frequent precursor of depression and that the efficacy of antidepressants for non-OCD anxiety disorders is larger than those for depression, identification and treatment of anxiety disorders may be another strategy to reduce the public health burden on child and adolescent

²⁰¹ *Id.* at 18 (statement of Rep. Stupak, Member, House Comm. on Energy and Com.).

depression.”²⁰² Acting early, in a preventive capacity, would be helpful in that fewer children, adolescents, and young adults would experience full-fledged depression. Moreover, as a result of this decline in the number of young, depressed individuals, there would be reduced usage of antidepressant medication to treat childhood mental illness. If we believe that there is any increased risk of suicidal ideation associated with pediatric antidepressants then the fewer youth who need this treatment, the better.

VII. CONCLUSION

In retrospect, it is unclear whether the black-box warning was necessary, given the strong response to the October 2003 letter to healthcare professionals and the March 2004 FDA health advisory. The black-box warning quickly became the target of criticism, but the decrease in pediatric antidepressant prescribing and the increase in youth suicide rates began prior to its issuance. Because the general public had already heeded the warnings found in the October 2003 advisory, the black-box warning may have been superfluous; it is very possible that the black-box warning was viewed merely as confirmation of what was already known rather than as a cautionary statement alerting the public to a new risk. As such, the black-box warning may not have been instrumental in the furtherance of the FDA’s mission of protecting the health and safety of Americans.

Of course, it takes years for prescription rate and suicide rate data to be collected and analyzed, so the FDA would not have been able to adjust its course of action based on these figures. To my knowledge, in October 2004, the FDA did not have any statistical information about the effects of its earlier advisories. Therefore, the FDA may have felt compelled to issue the black-box warning as a way of ensuring that its warning of increased risk of suicidality was

²⁰² Jeffrey A. Bridge et al., *Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials*, 297(15) J. AMER. MED. ASS’N 1683, 1693 (2007).

reaching the masses. It is easy in hindsight to recast the black-box warning as an unnecessary source of alarm; however, the FDA would never have issued its strictest warning unless it thought the warning to be important and beneficial to society.

Moreover, as was evidenced by the harsh comments from several Congresspeople during the congressional hearing entitled, “FDA’s Role in Protecting the Public Health: Examining FDA’s Review of Safety and Efficacy Concerns in Anti-depressant Use by Children,” the black-box warning may have been a political necessity. During the congressional hearing, the FDA was sharply criticized for insufficiently protecting the public from the risks of pediatric antidepressant drugs. Failing to issue the black-box warning may have resulted in the FDA being portrayed as a negligent agency. If the FDA had become regarded as an organization that was not dedicated to the protection of our people, the financial support the FDA received from Congress could have been significantly reduced and the general public would likely have lost confidence in the FDA. Therefore, while the black-box warning may not, in retrospect, have been necessary to protect the public from the perceived risks associated with pediatric antidepressant use, taking a firm stance on the protection of our youth may have been crucial from a political perspective.

While researchers remain conflicted as to the legitimacy of the claim that pediatric antidepressant use is associated with an increased risk of suicidality, and while the FDA’s statements with regard to this potential risk unexpectedly resulted in a higher rate of completed suicides in our country, one thing is clear: the FDA action was aimed at protecting the general public from what it perceived to be a significant risk. I have suggested several ways in which the FDA could have softened the blow of its warnings so as to inform the public of this risk without deterring vulnerable individuals from seeking needed treatment for their depression. However, I

remain convinced that once the FDA had concluded, based on its interpretation of the available data, that a link between pediatric antidepressant use and an increased risk of suicidality existed, it had no choice but to inform the public. I stand behind the FDA's decision to advise the public of its findings. If there is any fault to be found in the FDA's warnings, it is in the wording of its statements, not in the FDA's decision to issue the advisories or the black-box warning in the first place. A quote from B.F. Skinner, a renowned behaviorist and former Professor of Psychology at Harvard University, has what I believe is the best response to those who criticize the FDA action for its unintended consequences. He once said, "A failure is not always a mistake, it may simply be the best one can do under the circumstances. The real mistake is to stop trying."²⁰³

²⁰³ Goodreads, B.F. Skinner Quotes, http://www.goodreads.com/author/quotes/31631.B_F_Skinner (last visited January 20, 2011).